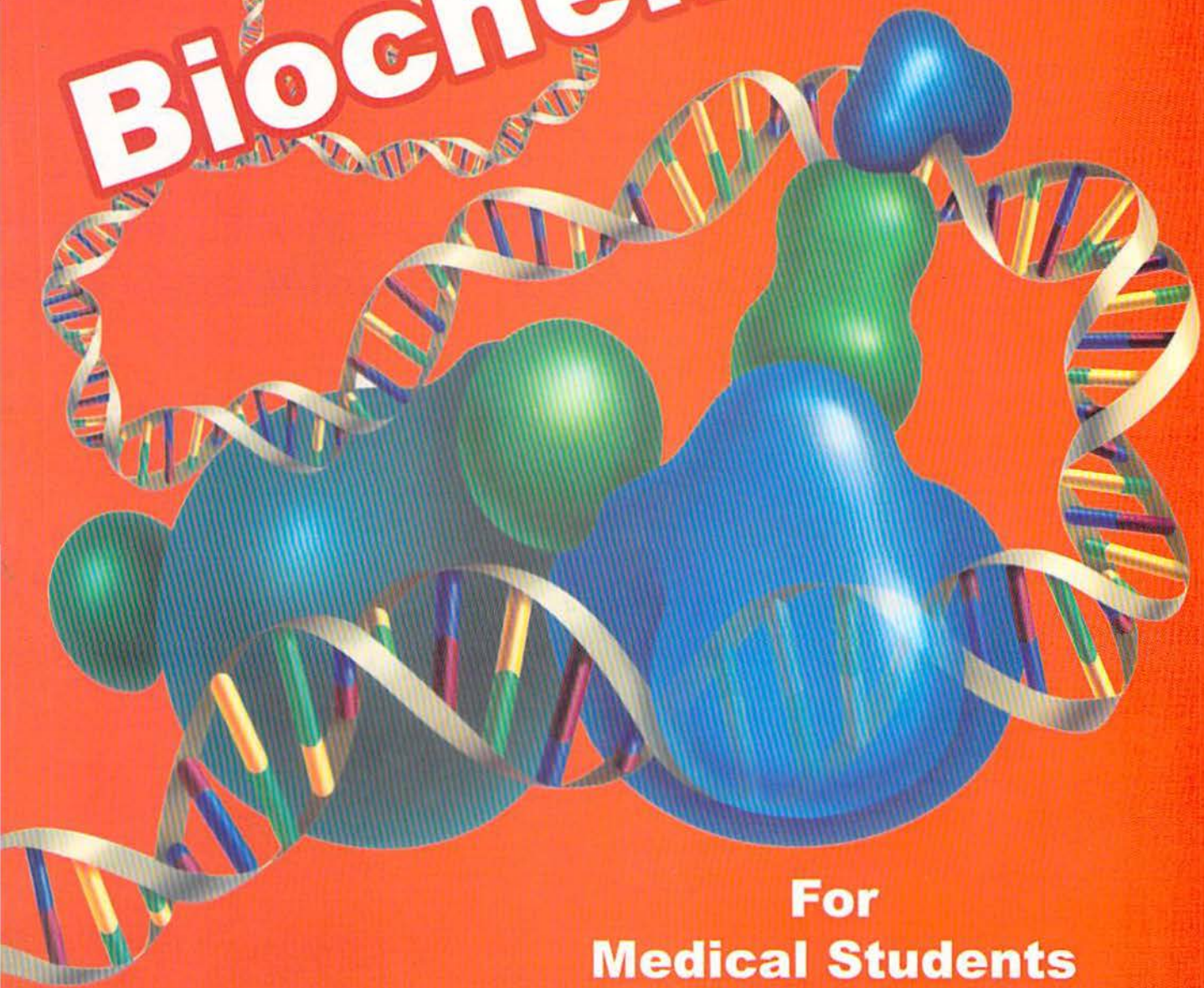
# Oraby's Illustrated Reviews of Biochemistry



For
Medical Students
and Postgraduates
Part I

# Oraby's Illustrated Reviews of

# Biochemistry

For Medical Students
And Postgraduates

By

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**( I )**

**Twelfth Edition**


قال العماد الأصفهانى

"إنى رأيتُ أنه لا يكتب إنسان كتاباً فى يومه إلا قال فى غده لو غُير هذا لكان أحسن، ولو زِيْدَ كذا لكان يُستحسنُ، ولو قُدم هذا لكان أفضل، ولو تُرك هذا لكان أجمل، وهذا من أعظم العبر، وهو دليلٌ على إستيلاء النقص على جُملة البشر."

## DEDICATION

**To my beloved daughter: Mariam, and my sons, the little tigers: Tarek and Hatem.**

## *Acknowledgments*

**Without the encouragement and participation of my students and colleagues, this work would never have been accomplished. My personal and very deep appreciation goes to each of them for sharing their ideas and making recommendations to improve the book, and for giving suggestions to modify it.**

**I am particularly indebted to late *Dr. Ahmed Shawky Fyzalla,* Professor of Medical Biochemistry, Al-Azhar Faculty of Medicine, Cairo, Egypt. He was a distinguished biochemist who had made a major personal effort to improve the teaching of biochemistry throughout Egypt.**

**Finally, a very special thanks to my loving supportive, and considerate *wife and family,* who had the foresight to encourage me to undertake this work, who again supported me during the days of intensive work, and who again created an environment in which I could devote the many hours in front of computer for preparation of this book. To her and my family my deepest appreciation.**

*Said Oraby*

***Note:***
***Dear student / colleague:***
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# *Oraby's illustrated reviews of Biochemistry*



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# Contents

# Contents of part II in brief

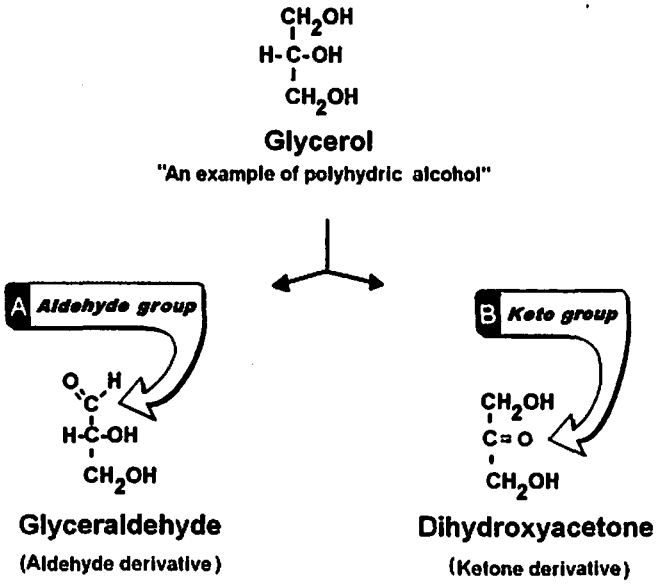


# Contents of part III in brief

# Chapter 1 *Carbohydrate Chemistry*

## I. *Definition:*

Carbohydrates are aldehyde or ketone derivatives of polyhydric alcohols or any substance derived from them.




## II. *Importance of carbohydrates:*

Carbohydrates are widely distributed both in plants and in animal tissues. In plants, they are produced by photosynthesis. Carbohydrates constitute about 60% of our diet. They are important for:

A. **Energy production** e.g. glucose.

B. Formation of **structural elements** in animal and plant cells.

C. Formation of **glycolipids** (carbohydrates combined with lipids) and **glycoproteins** (carbohydrates combined with protein); both enter in the structure of cell membrane and form the ground substances between tissues.

## III. *Classification of carbohydrates:*

A. **Monosaccharides**: contain one sugar unit.

B. **Disaccharides**: contain two sugar units.

C. **Oligosaccharides**: contain 3 – 10 sugar units.

D. **Polysaccharides**: contain more than 10 sugar units.

## IV. *Monosaccharides (glycoses):*

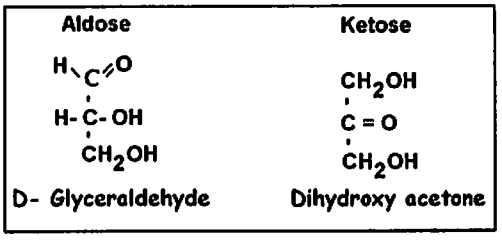
A. They are the **simplest** units of carbohydrate i.e. on hydrolysis, they can not give a simpler form. The general formula is **$Cn(H_2O)n$**.

B. **Naming (nomenclature) of monosaccharides:**

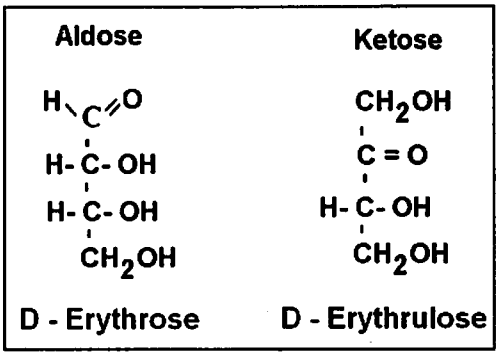
1. **According to the presence of aldehyde or ketone group:**
   a) **Aldoses**: monosaccharides containing aldehyde group (-CHO). The suffix **–ose** means sugar.
   b) **Ketoses**: monosaccharides containing ketone group (-C=O).
2. **According to the number of carbon atoms:**
   a) **Trioses**: monosaccharides containing 3 carbons.
   b) **Tetroses**: monosaccharides containing 4 carbons.
   c) **Pentoses**: monosaccharides containing 5 carbons.
   d) **Hexoses**: monosaccharides containing 6 carbons.
   e) **Heptoses**: monosaccharides containing 7 carbons.
3. **According to both presence of aldehyde or ketone groups and number of carbon atoms:**
   a) Aldotrioses and ketotrioses.
   b) Aldotetroses and ketotetroses.
   c) Aldopentoses and ketopentoses.
   d) Aldohexoses and ketohexoses.

C. **Classification of monosaccharides:**

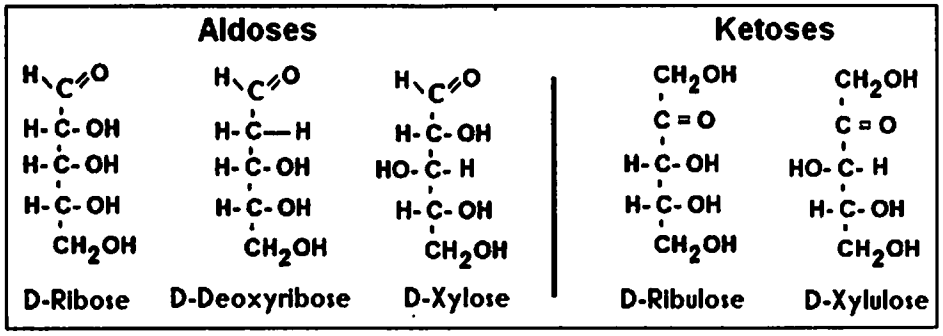
1. **Trioses**: monosaccharides containing 3 carbons.
   a) **Aldotrioses**: Glyceraldehyde "glycerose".
   b) **Ketotrioses**: Dihydroxyacetone.




2. **Tetroses**: monosaccharides containing 4 carbon atoms:
   a) **Aldotetroses:** Erythrose.
   b) **Ketotetrose:** Erythulose.
   **Note**: The suffix **–ulose** means **Keto** group.

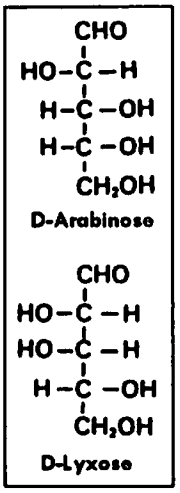



3. **Pentoses**: monosaccharides containing 5 carbon atoms.
   a) **Types:**
      1) **Aldopentoses**: Ribose, arabinose, xylose and lyxose.
      2) **Ketopentoses**: Ribulose and xylulose.




b) **Importance (functions) of pentoses:**

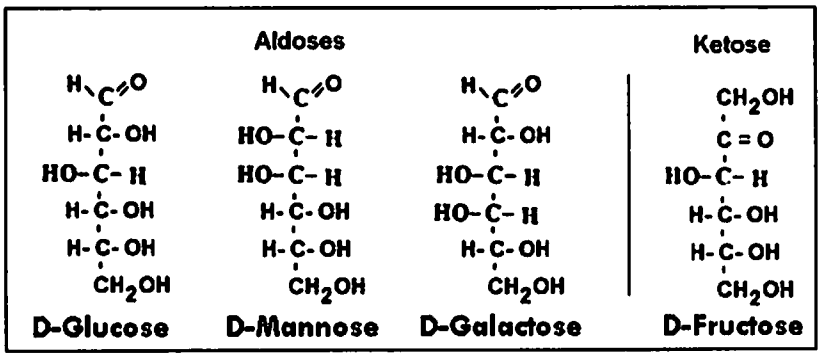
1) **Ribose and deoxyribose** enter in the structure of nucleic acids RNA and DNA.
2) **Ribose** enters in the structure of ATP, GTP and other high energy phosphate compounds.
3) **Ribose** enters in the structure of coenzymes NAD, NADP and flavoproteins.
4) **Ribose phosphate and ribulose phosphate** are intermediates in pentose phosphate pathway (a minor pathway for glucose oxidation).
5) **Arabinose and xylose** are constituents of glycoproteins in plants and in animals.
6) **Lyxose** is a constituent of a lyxoflavin isolated from human heart muscle.
7) **Xylulose** is an intermediate in uronic acid pathway (a minor pathway for glucose oxidation).




4. **<u>Hexoses:</u>** monosaccharides containing 6 carbon atoms

a) **Types:**

1) **Aldohexoses:** glucose, mannose and galactose.
2) **Ketohexose:** fructose.




b) **Importance:**

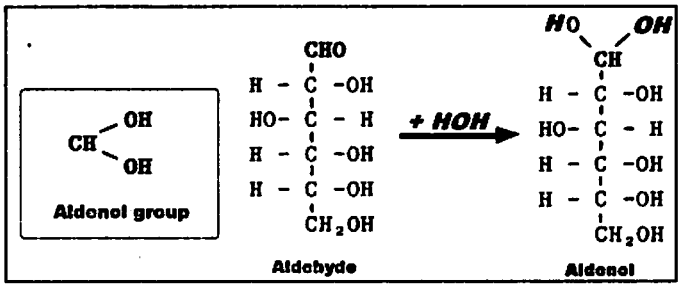
1) **Glucose** is the most important sugar of carbohydrate:
   - Glucose is the main sugar in blood.
   - Glucose is one of major sources of energy in the body.

- ➢ In the liver and other tissues, glucose is converted to all carbohydrates in the body e.g. glycogen, galactose, ribose and fructose.

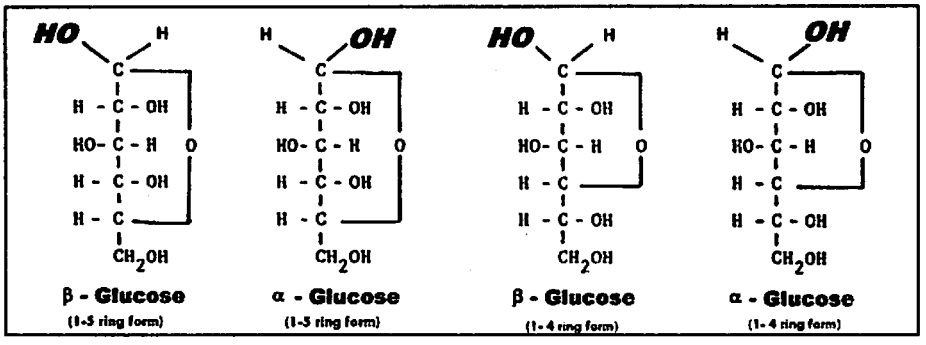
2) **Fructose "fruit sugar":**
   - ➢ It can be converted into glucose in the liver.
   - ➢ It is the main sugar of semen.
3) **Galactose:**
   - ➢ It can be converted into glucose in the liver.
   - ➢ It is synthesized in mammary gland to make the lactose of milk (milk sugar).
4) **Mannose:** A constituent of many glycoproteins.

D. **<u>Ring (cyclic) structure of sugars</u>:** The simple open chain formula of sugars fails to explain some reactions e.g. glucose, which has aldehyde group, does not give all the reactions of aldehyde. This indicates that the –CHO group must be masked or combined in some way. In solution, the sugar which has an aldehyde group undergoes the following:

1. **Hydration of aldehyde group to form aldenol group (alcohol).**
2. **Intra-molecular reactions occur by** subsequent condensation between one of the –OH of aldenol group and the –OH group of $C_4$ or $C_5$ to form ring structure (hemiacetal structure). Here, the carbonyl group becomes asymmetric carbon atom.

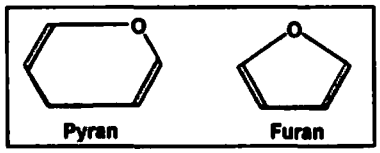



3. **If the remaining –OH is on the right side, it is α – sugar.**
   **If the remaining –OH is on the left side, it is β – sugar.**

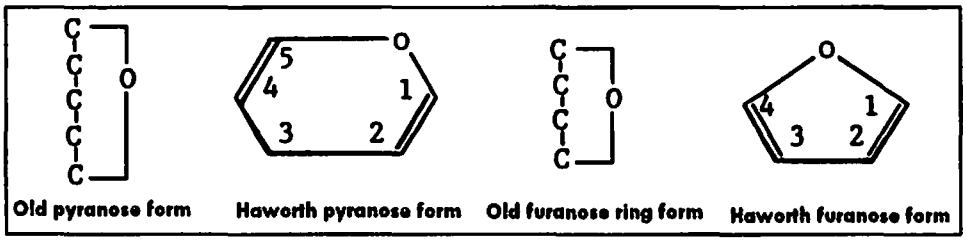



4. **Pyranose and furanose:**
   a) The 1-5 ring form is called **pyranose** as it resembles an organic compound called pyran e.g. α and β glucopyranose.

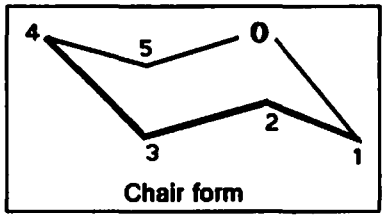
b) The 1-4 ring form is called **furanose** as it resembles an organic compound called furan e.g. α and β glucofuranose.



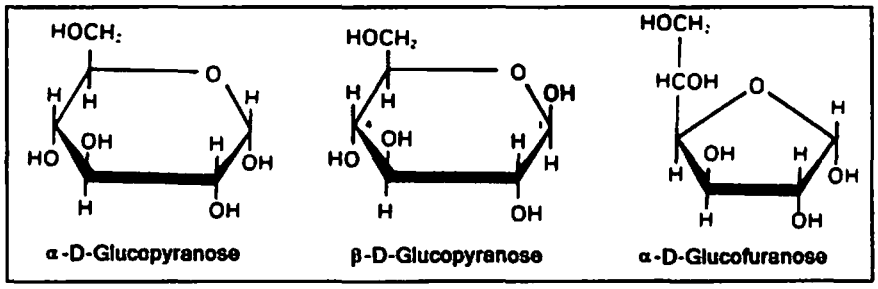

5. **Haworth and chair forms:**



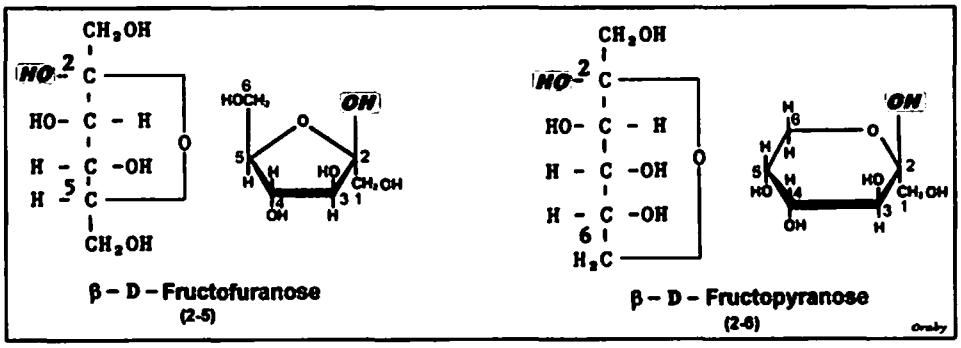

a) Cyclic structure of sugars may be present in the form of Haworth or chair forms. In Haworth formula, the arrangement of H and –OH groups around carbon atoms is as follows:

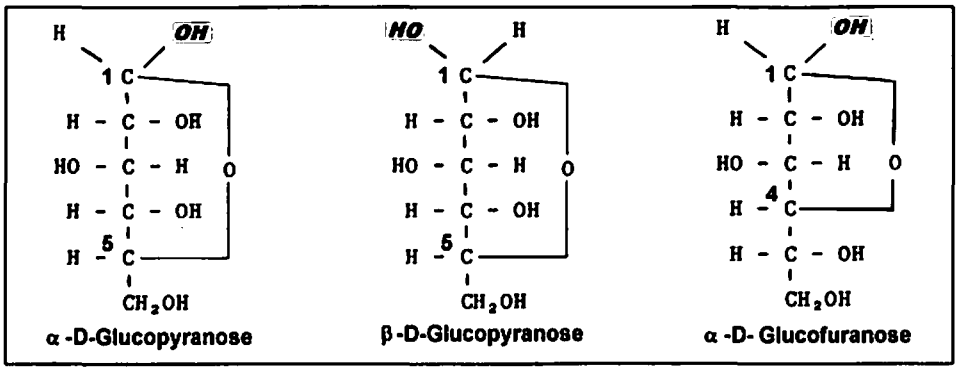



1) All the –OH groups on the right side in old ring structure are written downwards in Haworth formula.
2) All the –OH groups on the left side in old ring structure are written upwards in Haworth formula.
3) These rules are reversed at $CH_2$-OH groups e.g. last carbon atom of glucose that attached to oxygen i.e. $C_4$ in furanose and $C_5$ in pyranose.



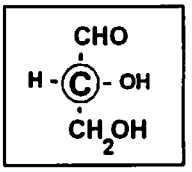

b) Glucose in solution is present mainly **(99%)** as **glucopyranose** and (1%) as glucofuranose. Of 99% of glucopyranose **(36%)** are present as **α – D** form and **(63%)** as **β –D form.**





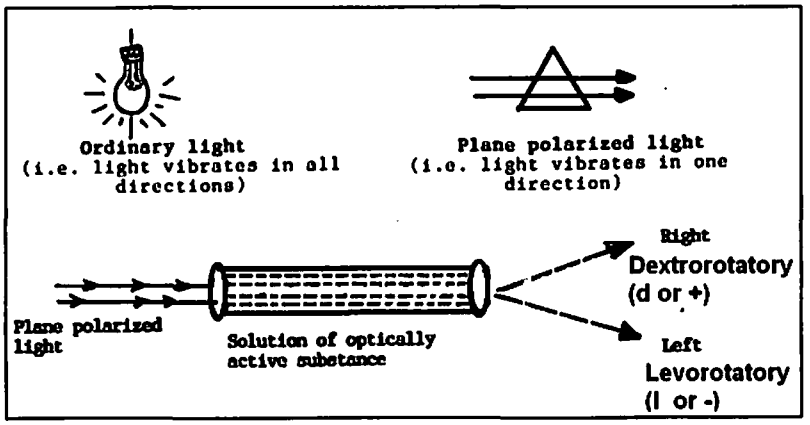

**V. *Asymmmetric carbon atom:* Is the carbon atom to which 4 different groups or atoms are attached.**

Any substance containing asymmetric carbon atom shows 2 properties, optical activity and optical isomerism.

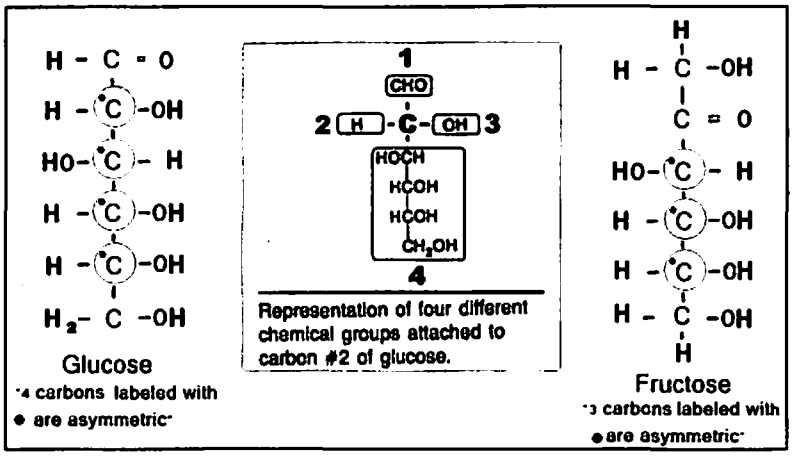



A. **Optical activity:**

It is the ability of substance to rotate plane-polarized light either to the right or to the left.




1. **If the substance rotates plane polarized light to the right so it is called:** dextrorotatory or d or (+). If it rotates it to the left so it is called: levorotatory or "l" or (-).
2. **Glucose contains 4 asymmetric carbon atoms.** It is dextrorotatory, so it is sometimes named **dextrose**. Fructose contains 3 asymmetric carbon atoms. It is levorotatory so it is sometimes called: **Levulose**.

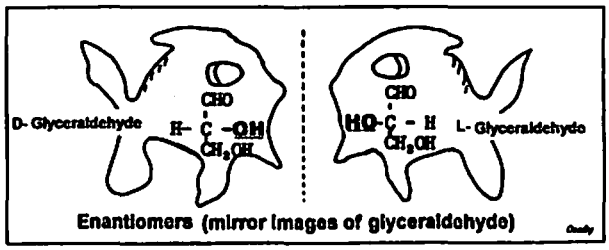


3. **Specific rotation:**
   **It is the angle of rotation specific for each optically active substance when:**
   a) The concentration of substance is 100 g/dl.
   b) The length of measuring tube is 10 cm e.g. specific rotation for glucose is (+52.5°) and for fructose is (-91°).
4. **Racemic mixture:**
   It is the mixture containing equal number of molecules of 2 optically active sugars, one is dextrorotatory and the other is levorotatory. Thus, it shows no optical activity (provided that the angle of rotation is equal in both sides).
5. **Resolution:**
   It is the separation of optically inactive racemic mixture into its optically active substances.

B. **<u>Optical isomerism</u>: It is the ability of substance to present in more than one form (isomer).**

- A substance containing one asymmetric carbon atom has 2 isomers.
- A substance containing 2 or more asymmetric carbon atoms can exist in a number of isomers $=2^n$ where n is the number of asymmetric carbon atoms. E.g. glucose has 4 asymmetric carbon atoms so the number of its isomers equal $2^4 = 2 \times 2 \times 2 \times 2 = 16$ isomers.

1. **Configuration (Enantiomers):**
   a) The simplest carbohydrate is glyceraldehyde that has one asymmetric carbon atom. So it has 2 optically active forms: L and its mirror image D forms.

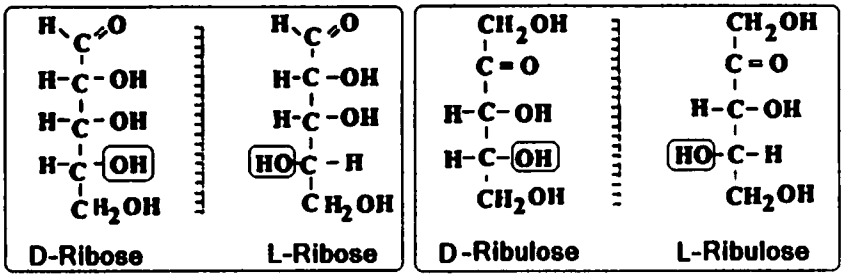


Enantiomers (mirror images of glyceraldehyde)

   b) **Reference sugar:**
   It is the ***glyceraldehyde*** which may be present in
   - ***(D)*** form in which –OH group attached to asymmetric carbon atom is on the right side.
   - ***(L)*** form in which –OH group attached to asymmetric carbon atom is on the left side.

   1) **All other monosaccharides are considered to be derived from reference sugar glyceraldehyde.** They are classified into D and L forms according to the position of –OH attached to the carbon atom next to last $-CH_2OH$ e.g. carbon atom number 5 in glucose.
   2) Most of the monosaccharides occurring in mammals are of D configuration (form).

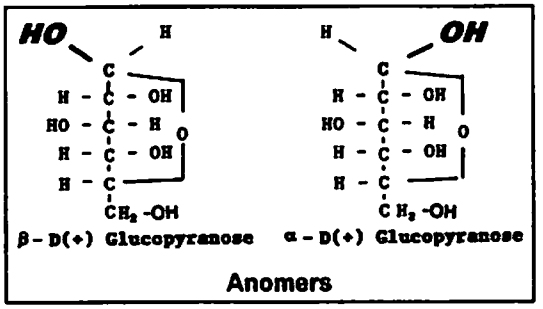
3) A sugar may be dextrorotatory (d) or levorotatory (l) irrespective of its D or L forms.




2. **Anomeric carbon and anomers:**

a) **Anomeric carbon**: is the asymmetric carbon atom obtained from active carbonyl sugar group: carbon number 1 in aldoses and carbon number 2 in ketoses.

b) **Anomers**: These are isomers obtained from the change of position of hydroxyl group attached to the anomeric carbon e.g. α and β glucose are 2 anomers. Also α and β fructose are 2 anomers.

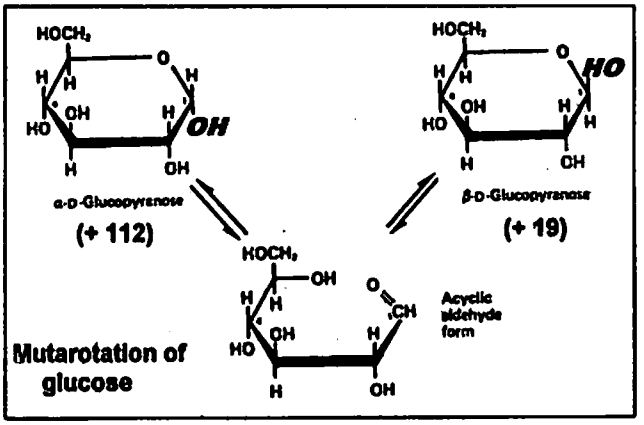



c) **Mutarotation:**

1) **It is a gradual change of specific rotation of any optically active substance having free aldehyde (-CHO) or ketone (C=O) group (i.e. having anomeric carbons).**

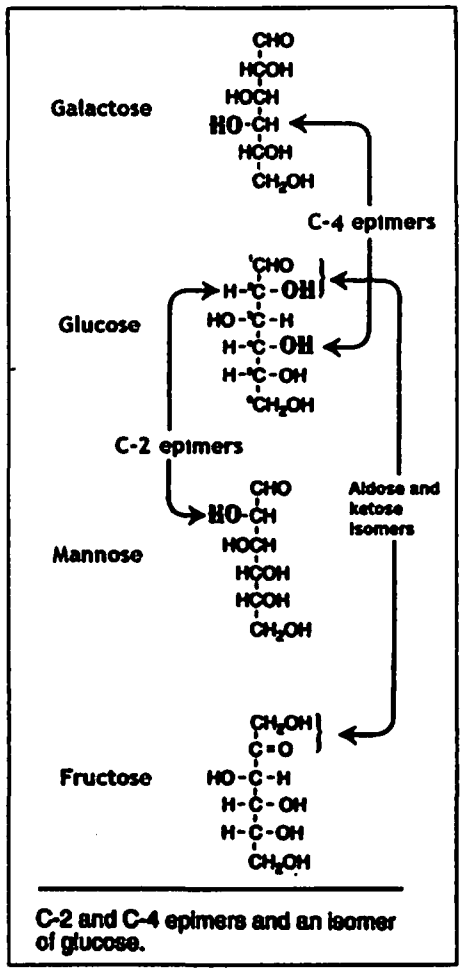
2) α–Glucose When freshly dissolved in water, has specific rotation of +112.

3) β – Glucose when freshly dissolved in water, has specific rotation of +19.




4) When both anomers are left for sometimes, α and β sugars are interconvert and slowly change into an equilibrium mixture of α, β and open chain glucose which has specific rotation of + 52.5.

3. **Aldose-Ketose isomerism**: Fructose has the same molecular formula as glucose but differs in structure formula. One contains keto group (C=O) and the other contains aldehyde group (-CHO). Both are isomers.
4. **Epimeric carbon and epimers**:
   a) **Epimeric carbon is** the asymmetric carbon atom other than carbon of aldehyde or ketone group e.g. carbons number 2,3 and 4 of glucose.
   b) **Epimers**: are isomers resulting from the change of position of groups around the epimeric carbons. Glucose, galactose and mannose are epimers.
      1) **Glucose** has 3 epimeric carbons 2, 3 and 4.
      2) **Galactose**: epimer of carbon 4.
      3) **Mannose**: epimer of carbon 2.



C-2 and C-4 epimers and an isomer of glucose.

## VI. *Properties of monosaccharides:*

A. **Physical properties**:

1. All monosaccharides are soluble in water.
2. All monosaccharides show the property of optical activity.
3. All monosaccharides can exist in α and β forms.
4. All monosaccharides can undergo mutarotation.

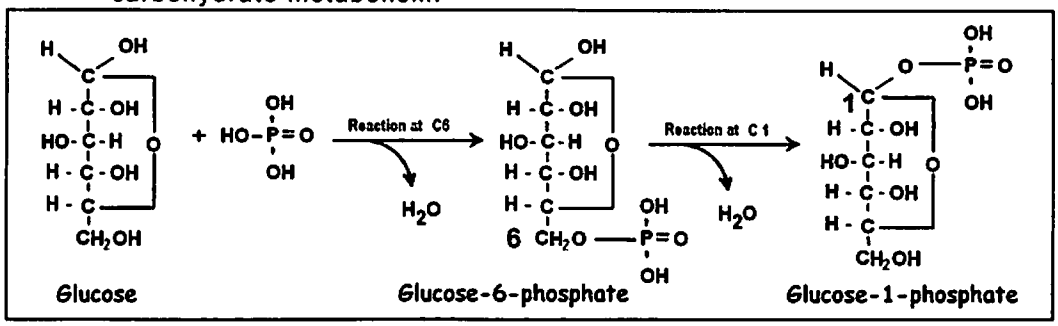
B. **Chemical properties**:

1. **Oxidation**: Oxidation of sugars gives acids (see sugar derivatives)
2. **Reduction**: Reduction of carbonyl group gives the corresponding alcohol e.g. glucose gives sorbitol, ribose gives ribitol, galactose gives galacticol etc.
3. **Reducing sugars**: Sugars containing free aldehyde or ketone group can reduce other reagents e.g. they can reduce cupric ions of Fehling's and Benedict's reagents into cuprous ions:

   Cupric (**blue**) + sugar → Cuprous (**red**) + oxidized sugar

   a) These tests are one of the earliest tests for sugar detection in urine of diabetics.
   b) These tests are **nonspecific**, because these reagents can be reduced also by other hexoses or other reducing compounds as vitamin C.

4. **Reactions of phosphoric and sulfuric acids:**
   a) Reaction of phosphoric acid with monosaccharides gives phosphate esters e.g. glucose gives glucose-6-phosphate and glucose-1-phosphate. Phosphorylated sugars are important intermediates in carbohydrate metabolism.




   b) **Reaction of sulfuric acids**: This acid is a dehydrating agent, removing 3 molecules of $H_2O$ from the sugar giving a compound called **furfural**. This compound can condense with **α–naphthol** to give a violet ring. This is the idea of ***Molish's test***, a general test for all carbohydrates.

5. **Fermentation**: Fermentation is the action of bacterial or yeast enzymes on carbohydrate.
   a) Fermentation of sugars give ethyl alcohol and $CO_2$.
   b) All D-monosaccharides are fermentable.

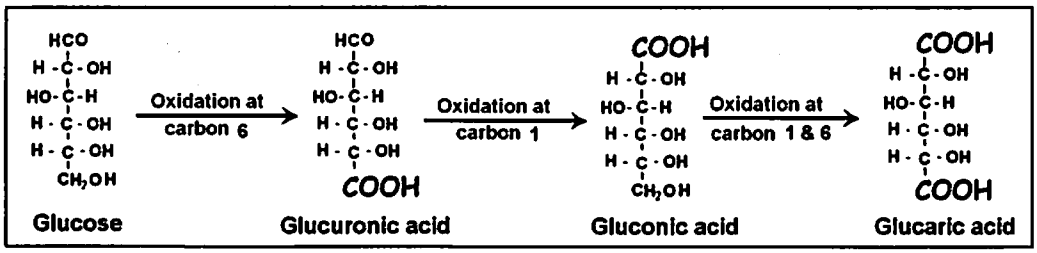
$$C_6H_{12}O_6 \rightarrow 2\ CH_3\text{-}CH_2\text{-}OH + 2\ CO_2$$

Hexose Ethyl alcohol Carbon dioxide

6. **Osazone formation**: Osazones are characteristic crystals resulting from the reaction of sugars with phenylhydrazine. All sugars having free carbonyl group can form osazone crystals.

## VII. *Sugar derivatives:*

A. **Sugar acids**: are produced by oxidation of carbonyl carbon, last hydroxyl carbon or both.

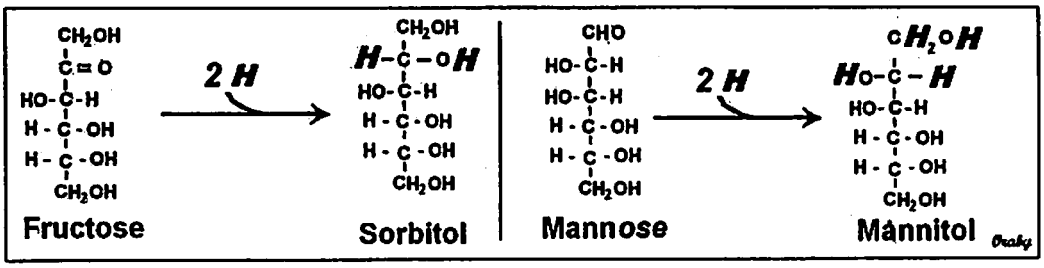



1. **Aldonic acids**: oxidation of carbonyl carbon to carboxylic group gives aldonic acid e.g. glucose is oxidized to gluconic acid.
2. **Uronic acids**: oxidation of last hydroxyl carbon gives uronic acid e.g. glucose is oxidized to glucuronic acid.

3. **Aldaric acids**: These are dicarboxylic acids produced by oxidation of both carbonyl carbon and last hydroxyl carbon e.g. glucose is oxidized to glucaric acid (saccharic acid).

B. **Sugar alcohols**: Monosaccharides, both aldoses and ketoses may be reduced at carbonyl carbon, to the corresponding alcohol:

1. Glucose is reduced to sorbitol (glucitol), galactose is reduced to galacticol (dulcitol), mannose is reduced to mannitol.
2. Fructose is reduced to mannitol and sorbitol.
3. Ribose is reduced to ribitol, a constituent of vitamin $B_2$ (riboflavin) and coenzyme FAD.

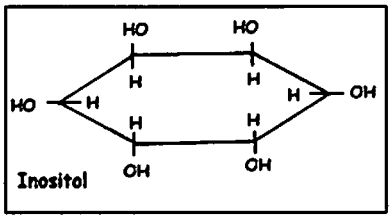



4. **Inositol = cyclitol**

a) It is a sugar derived from glucose.

b) **Functions:**

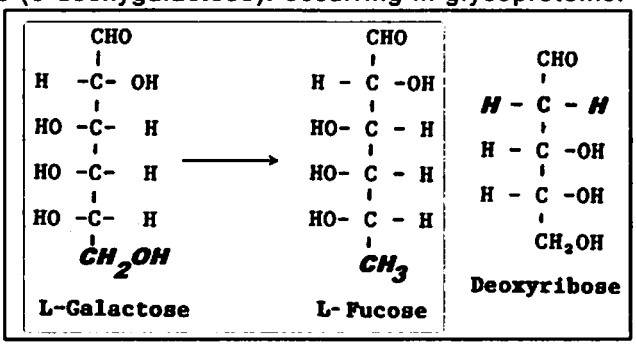
1) Inositol enters in the structure of lipositol (a phospholipid), which is present in cell membrane.




2) It acts as precursor of second messenger (inositol triphosphate), mediating hormonal action inside cells.

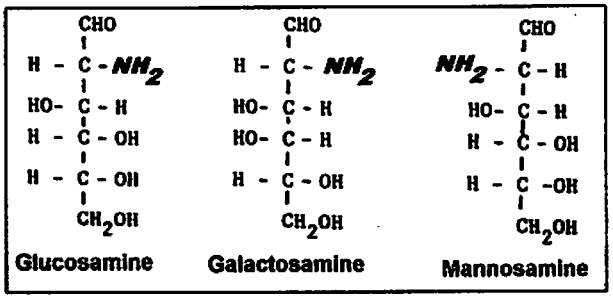
C. **Deoxysugars:**

1. Are sugars in which one of the hydroxyl groups has been replaced by a hydrogen atom i.e. one oxygen is missed.
2. **Deoxyribose**: occurring in nucleic acid DNA.
3. **L-Fucose** (6-deoxygalactose): occurring in glycoproteins.

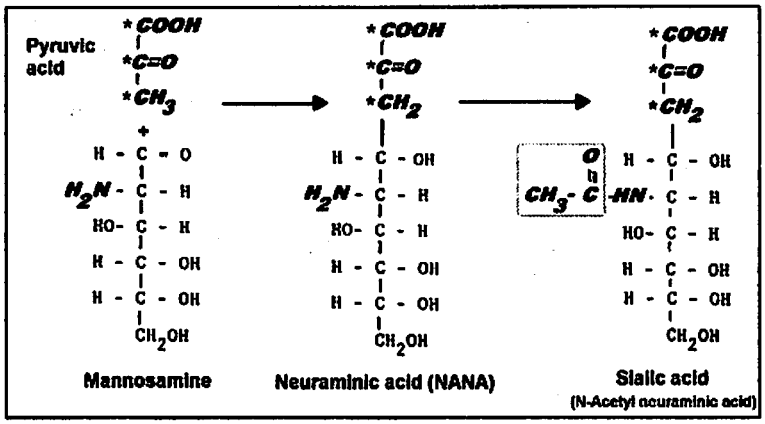



D. **Amino sugars**: in these sugars, the hydroxyl group attached to carbon number 2 is replaced by an amino or an acetylamino group.

1. Amino sugars are constituents of glycoproteins, gangliosides and glycosaminoglycans.
2. **Examples:**
   a) **Glucosamine:** It occurs in heparin and hyaluronic acid.
   b) **Galactosamine:** It occurs in chondroitin sulphate.
   c) **Mannosamine:** It occurs in neuraminic and sialic acids.

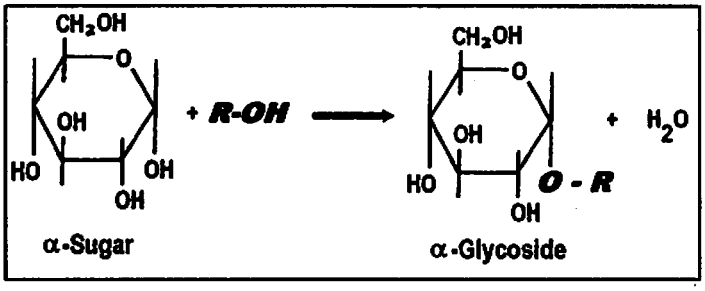



E. **Amino sugar acids:**
1. These are a condensation of amino sugars and some acids.
2. They are occurring in glycoproteins.
3. Examples include neuraminic acid (NANA) and sialic acid which is N-acetyl neuraminic acid.

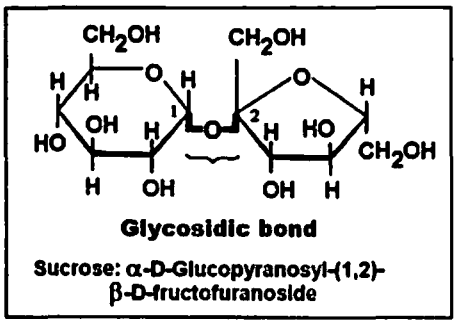



## VIII. *Glycosidic bond and glycosides:*

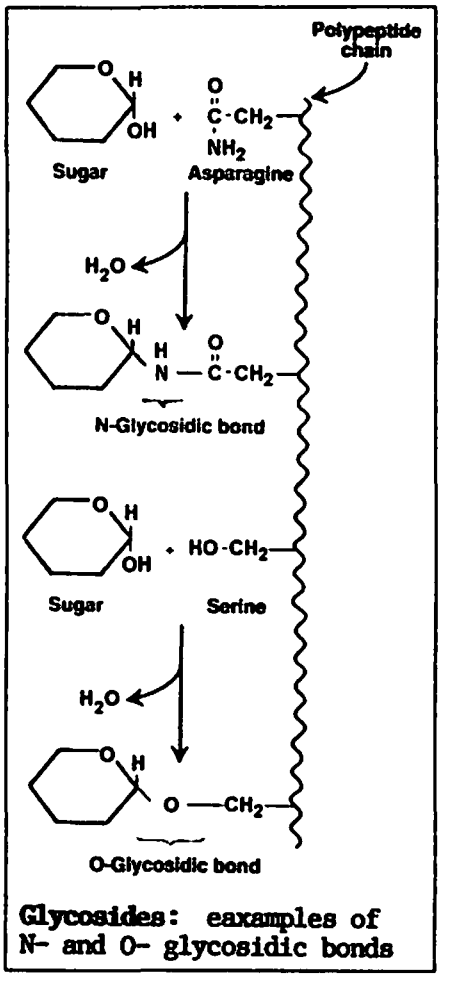
A. **Glycosidic bond:** It is the bond between a carbohydrate and another compound to form a complex carbohydrate.




1. This bond is between the hydroxyl group of anomeric carbon of monosaccharide (carbon 1 in aldoses or carbon 2 in ketoses) and another compound which may be:
   a) **Another monosaccharide** to form disaccharide glycosides as maltose, lactose and sucrose.
   b) **Aglycone i.e.** non-carbohydrate to form glycoside.




2. **N and O-glycosides:**
   a) If the monosaccharide is attached to –OH group of another sugar or aglycone, the resulting structure is an O-glycoside and the bond is called acetal link.
   b) If the monosaccharide is attached to –NH2 of aglycone, the resulting structure is N-glycoside.
   c) All sugar-sugar glycosidic bonds are O type linkage. If the first sugar is glucose, the resulting compound is **glucoside**, if galactose, a **galactoside** and so on.




**Glycosides:** examples of N- and O- glycosidic bonds

B. **Examples of glycosides**:
1. Disaccharides: discussed later.
2. Sugar nucleotide as ATP, GTP and other nucleotides: aglycone here is purines and pyrimidines.
3. **Glycolipids**: as cerebrosides.
4. **Glycoproteins.**
5. **Cardiac glycosides:**
   a) Aglycone here is steroid.
   b) Cardiac glycosides such as digitalis are important in medicine because of their action on heart.

## IX. *Disaccharides:*

These are formed by condensation of 2 molecules of monosaccharides bound together by glycosidic bond. Its general formula is $C_n(H_2O)_{n-1}$.

A. **The most important disaccharides are**:
1. **Maltose** = α-glucose + α-glucose **(α 1 – 4 glycosidic bond ).**
2. **Isomaltose** = α- glucose + α-glucose **(α 1 – 6 glycosidic bond).**
3. **Lactose** = β- glucose + β- galactose **( β 1 – 4 glycosidic bond).**

4. **Sucrose** = α-glucose + β-fructose **(α 1 – β 2 glycosidic bond).**
5. **Cellobiose** = β- glucose + β-glucose **(β 1 – 4 glycosidic bond).**
6. **Trehalose** = α- glucose + α-glucose **(α 1 – 1 glycosidic bond).**

B. **Naming (Nomenclature) of glycosidic bonds:** Glycosidic bonds between sugars are named according to:

1. The numbers of the connected carbons.
2. The position of the anomeric carbon of the sugar. If it is in α position, the linkage is an α- bond. If it is in the β position, the linkage is a β-bond.
3. **Example**: Lactose consists of β-glucopyranose and β-galactopyranose. The bond is between carbon 1 of β-galactopyranose and carbon 4 of glucopyranose. The bond is therefore β 1 – 4 galactosidic linkage.

C. **Maltose**: Also called malt sugar:

1. **Structure**: it is formed of 2 molecules of α-D glucopyranose linked together by α 1 – 4 glycosidic bond.
2. **Sources:**
   a) Malt.
   b) Maltose is produced during digestion of starch by amylase enzyme.
3. **Properties**: Maltose contains **free carbonyl** (aldehyde) group, so having the following properties:
   a) It is a **reducing agent** (can reduce Benedict's reagent).
   b) It can be present in **α** and **β** forms.
   **c) It can show mutarotation.**
   d) It can form characteristic **osazone** crystals.

D. **Isomaltose:**

1. **Structure**: It is similar to maltose, being formed of 2 molecules of α-D glucopyranose, but linked together by α 1 – 6 glycosidic bond.
2. **Sources**: isomaltose is produced during digestion of starch and glycogen by amylase enzyme.
3. **Properties**: The same as maltose.

E. **Lactose:**

1. **Structure**: It is formed of 2 molecules of β-D-galactopyranose and β-D-glucopyranose linked together by β 1-4 glycosidic (galactosidic) bond.
2. **Sources:** It is the sugar present in milk. In human milk, its concentration is 7.4 g/dl. It may appear in urine in late pregnancy and during lactation.
3. **Properties:** lactose contains free carbonyl group, so having the following properties:
   a) It is **reducing sugar** (can reduce Benedict's reagent).

b) It can be presented in **α and β forms**.

c) It can show **mutarotation.**

d) It can form characteristic **osazone** crystals.

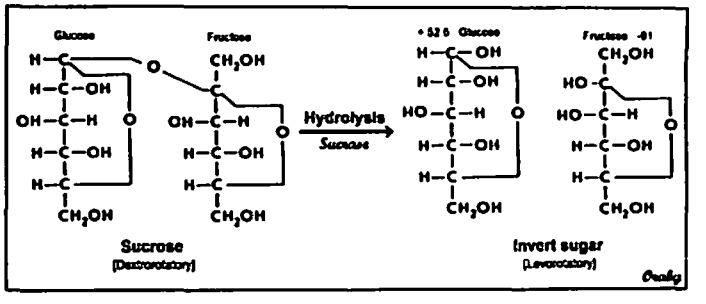
e) Lactose is digested by intestinal enzyme called: lactase into galactose and glucose. Deficiency of this enzyme stops the digestion of lactose. This leads to its fermentation by intestinal bacteria, diarrhea and abdominal distension.

F. **Sucrose**:

1. **Structure**: it is formed of 2 molecules of α –D- glucopyranose and β-D-fructofuranose linked together by α 1 ⟹ β 2 glycosidic bond.
2. **Sources**: cane and beet sugar. It is also present in pineapple and carrot.
3. **Properties**: sucrose contains **no free carbonyl group** (because both the anomeric carbons; carbon 1 of α-glucose and carbon 2 of β-fructose are involved in glycosidic bond) so fructose has the following properties:
   a) It is not a reducing sugar (cannot reduce Benedict's reagent).
   b) It cannot be present in **α and β forms**.
   c) It cannot show **mutarotation.**
   d) It cannot form **osazone** crystals.
   e) Sucrose is **dextrorotatory**. On hydrolysis by invertase (sucrase) enzyme, it gives a mixture of equal number of glucose and fructose molecules. This mixture is called **invert sugar** and it is levorotatory.

G. **Invert Sugar :**

1. **Structure**: It is a sugar that contains equal number of both glucose and fructose molecules (unbound).
2. **Sources:**
   a) **Bee honey**.
   b) **By hydrolysis of sucrose** by sucrase (invertase) enzyme.




3. **Properties**:
   Invert sugar contains free carbonyl groups, so it has the same properties as lactose and maltose (it is reducing, can be present in α and β forms, show mutarotation and can form osazone crystals).

H. **Trehalose**:

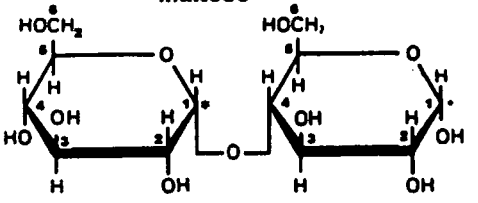
1. **Structure**: It is non-reducing sugar, formed of 2 units of α –D glucopyranose linked together by α 1 ⇒ 1 glycosidic bond.

2. **Sources:** It is present in fungi and yeast.
3. **Importance:** Trehalose can be used as a sweetener and **preservative** for foods. It can be also used in organ and tissue preservation solutions that provide improved viability of an organ such as a heart or lung.

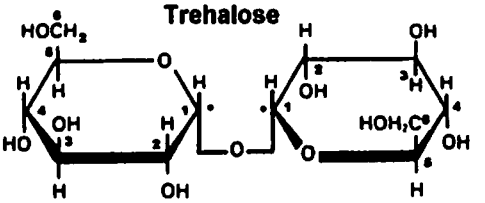
I. **Cellobiose**:

1. **Structure:** It is formed of 2 units of β-D glucopyranose linked by β 1-4 Glycosidic bond.
2. **Sources:** It is obtained by partial hydrolysis of cellulose present in plants.

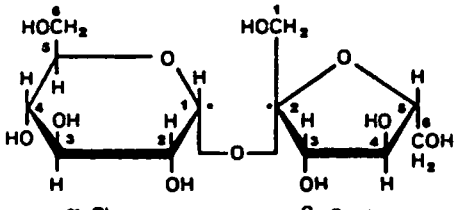
**Maltose**




**Trehalose**

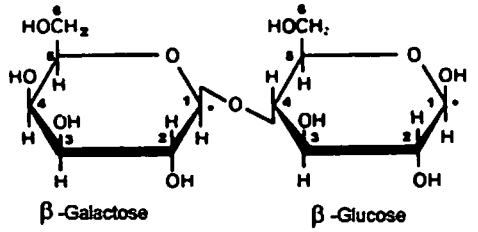



**Sucrose**

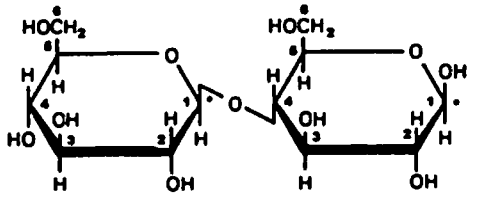



## *Disaccharides*

**Lactose**



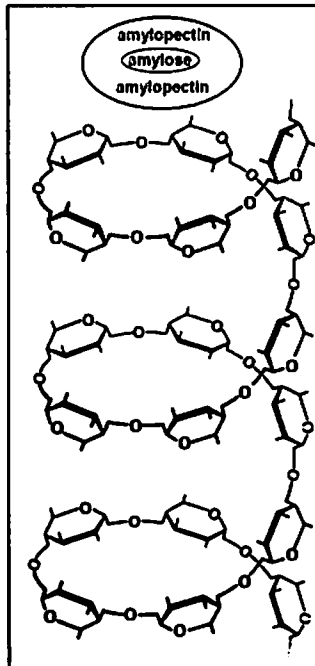

**Cellobiose**



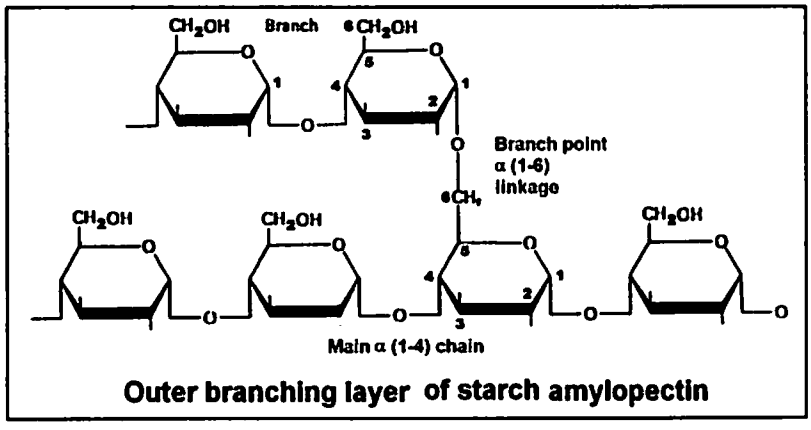

X. ***Polysaccharides***: These are carbohydrates, formed of more than 10 sugar units. They are classified into: homopolysaccharides and heteropolysaccharides.

A. **Homopolysaccharides**: They contain repeated **same** sugar units and include: starch, dextrins, glycogen, cellulose, inulin and dextrans.

1. **Starch** (also called **glucosan** or **glucan**):
   a) **Structure**: Starch granule is formed of inner (amylose) and outer (amylopectin) layers:
      1) **Inner layer**: called **amylose**. It constitutes 15-20% of the granule and formed of non-branching helical structure of glucose units linked together by α 1 – 4 glycosidic bond.
      2) **Outer layer**: called **amylopectin**. It constitutes 80-85% of the granule and formed of branched chain. Each chain is composed of 24-30 glucose units linked together by α 1 – 4 glycosidic bond and α 1 – 6 glycosidic bond at the branching points.



Inner layer of starch (amylose).

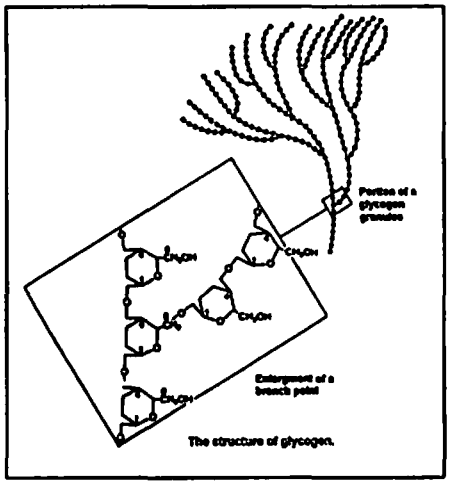


Outer branching layer of starch amylopectin

   b) **Sources**: cereals, potatoes, legumes and other vegetables.
   c) **Functions**: starch is the main carbohydrate content in our diet. It constitutes about 60% of our daily ingested food.
   d) **Properties**:
      1) Starch gives blue color with iodine. Amylopectin gives red color with iodine.
      2) Partial hydrolysis (digestion) by amylase enzyme gives various forms of dextrins.

2. **Dextrins**: These are hydrolytic products of starch. They are formed of α-glucose units but simpler than starch. They include amylodextrin, erythrodextrin and achrodextrin. They give red color with iodine.

3. **Glycogen:** (also called animal starch):

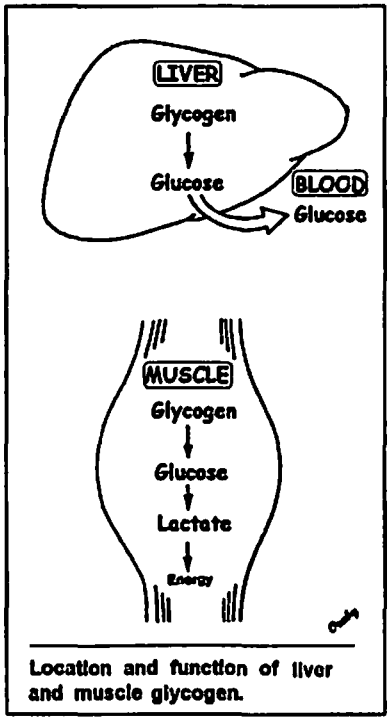



a) **Structure:**
   1) Glycogen is homopolysaccharide formed of branched α D glucose units (α 1,4 and α 1,6).
   2) The main glycosidic bond is α1-4-linkage. Only at the branching point, the chain is attached by α1-6 linkage.
   3) Each branch is made of 12-14 glucose units.

b) **Location:** Glycogen is present mainly in liver and muscles.

c) ***Functions of glycogen:***
   1) **Liver glycogen:** It maintains normal blood glucose concentration especially during the early stage of fast (between meals). After 12-18 hours fasting, liver glycogen is depleted.
   2) **Muscle glycogen:** It acts as a source of energy within the muscle itself especially during muscle contractions.

d) **Properties:** It gives reddish violet color with iodine.




**Location and function of liver and muscle glycogen.**

4. **Cellulose:**

a) **Structure:** It is long straight nonbranching chains of β-glucose units linked together by β 1-4 glycosidic bond.

b) **Sources:** Cellulose is the chief constituent of the framework of plant, leafy vegetables, fruits, wood, cotton, etc.

c) **Properties:**
   1) Cellulose gives no color with iodine.
   2) Cellulose is insoluble in water.
   3) Many mammals including humans cannot digest cellulose of diet because of the absence of digestive ***hydrolase*** enzyme that attacks β-linkage.

d) **Importance:**
   1) The presence of cellulose in diet is important because it increases the bulk of stool. This stimulates intestinal movement and prevents constipation.
   2) Cellulose is a constituent of dietary fibers. These fibers help in decreasing absorption of toxic compounds and reduce the incidence of cancer colon. For details see chapter of nutrition.

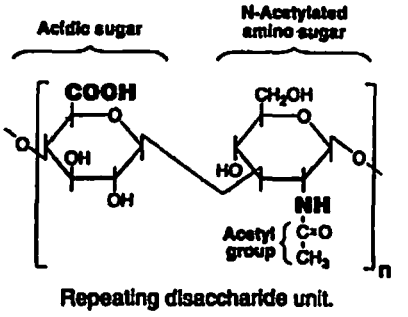
e) Cellulose can be utilized and serve as a source of energy in herbivores because their gut contains bacterial enzyme that can attack β-linkage.

5. **Inulin:**
   a) **Structure:** It is fructosan i.e. formed of repeated units of fructose linked together by β 1-2 bonds.
   b) **Sources:** Root of artichokes and other plants.
   c) **Medical Importance:** Inulin clearance is one of diagnostic tests for investigation of glomerular filtration rate.
6. **Dextrans:**
   a. **Structure:** It is branched chain homopolysaccharide. Each branch is composed of glucose units, linked together by α 1-3 glycosidic bonds and by α 1-6 glycosidic bond at branching point.
   b. **Sources:** dextran is synthesized from sucrose by certain bacteria.
   c. **Functions:** Dextran is used as plasma substitute and prevents thrombosis.

B. **Heteropolysaccharides:** They contain repeated different sugar units and include glycosaminoglycans.

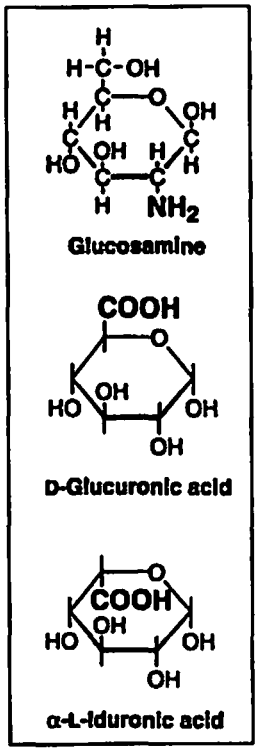
## XI. *Glycosaminoglycans, GAGs (mucopolysaccharides):*

### A. Introduction:

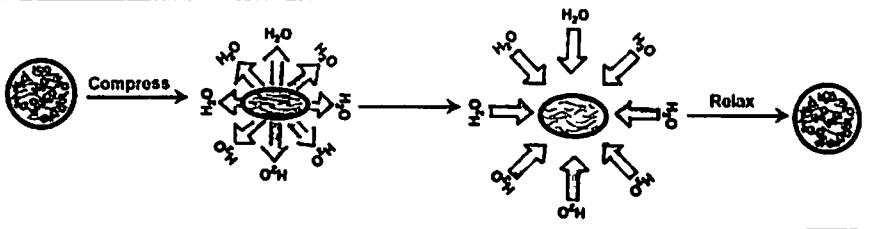


Repeating disaccharide unit.

1. They are formed of repeating disaccharide units (acidic sugar-amino sugar)$_n$.
   a) The acidic sugar is either D-glucuronic acid or its epimer, L-induronic acid.
   b) The amino sugar is either D-glucosamine or D-galactosamine in which the amino group is usually acetylated. The amino sugar may also be sulfated at carbon 4 or 6.
2. GAGs often contain sulfate groups. The uronic acid and sulfate residues cause them to be very negatively charged.
3. They are unbranched.
4. Most of GAGs are present extracellularly except heparin.
5. Most of them form the structural components of connective tissue such as bone, elastin and collagen.
6. They act as lubricants and cushion for other tissues because they have the property of holding large quantities of water.
7. When a solution of glycosaminoglycans is compressed, the water is "squeezed out" and the glycosaminoglycans are forced to occupy a smaller volume, when the compression is released, the



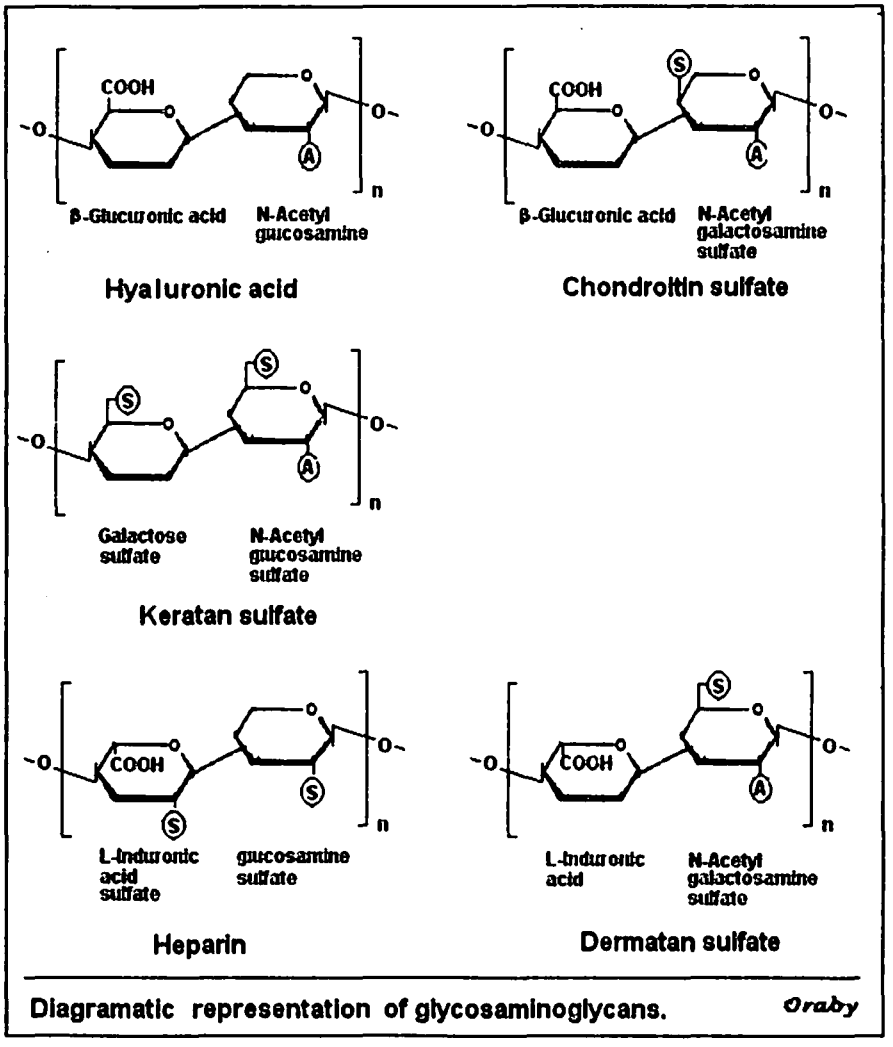
glycosaminoglycans return to their original, hydrated volume because of the repulsion of their negative charges. This property is the cause of resilience of synovial fluid and the vitreous humor of the eye.




Resilience of glycosaminoglycans

B. **Glycosaminoglycans include:**

1. **Hyaluronic acid.**
2. **Chondroitin 4 – and 6 sulfate.**
3. **Keratan sulfate.**
4. **Dramatan sulfate.**
5. **Heparin and heparan sulfate.**



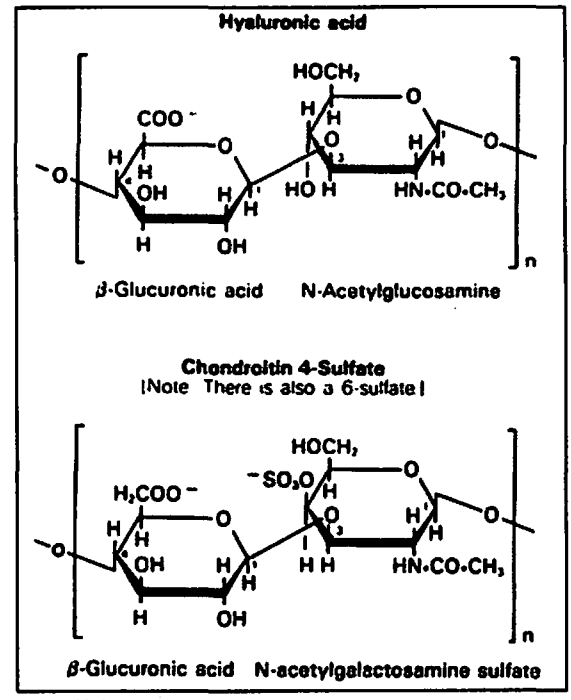

Diagramatic representation of glycosaminoglycans. *Oraby*

1. **Hyaluronic acid:**

**a) Structure:** Repeated disaccharide units consists of:

1) Glucuronic acid.
2) N-acetylglucosamine.

N.B Hyaluronic acid is the only GAGs which contains **no sulfate** group.




**b) Site:**

1) Cartilage.
2) Connective tissue.
3) Synovial fluid.
4) Vitreous humor of the eye.
5) Embryonic tissue.

**c) Functions:**

1) It acts as a lubricant in joints.
2) It makes cartilage **compressible**
3) It makes extracellular matrix **loose** because of its ability to attract water.
4) It permits cell migration during **wound repair.**
5) It permits cell migration during **morphogenesis,** i.e. differentiation of cells in the form of organs and tissues in the early embryo.

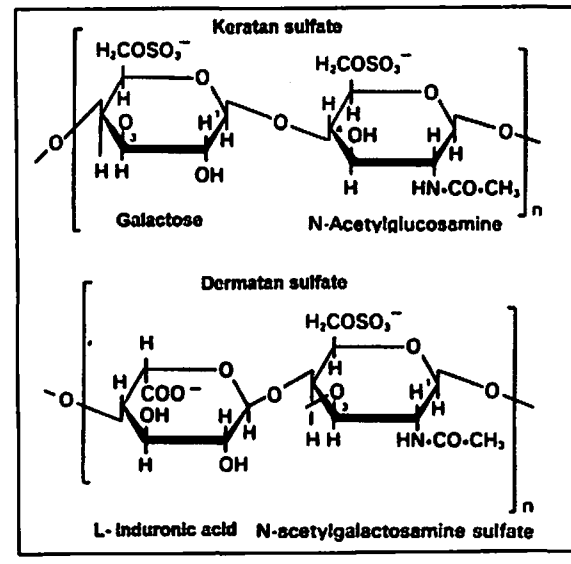
**d) Role in disease:**

Hyaluronic acid facilitates cell migration. It is produced in increased amounts by tumor cells. This facilitates migration of these cells through the extra cellular matrix and spread of the tumor.

2. **Chondroitin 4 – and 6 sulfate:**

**a) Structure:** It is usually present in association with protein to form proteoglycan aggregates. The repeated disaccharide unit consists of:

1) Glucuronic acid.
2) N-acetylgalactosamine with sulfate on either $C_4$ or $C_6$.



b) **Site**: It is the most abundant GAGs in the body. It is found in:

1) Cartilage, tendons, ligaments and bones.
2) Aorta, skin, cornea, umblical cord and in certain neurons.

c) **Functions:**

1) In cartilage: it binds collagen and hold fibers in strong network.
2) It makes cartilage **compressible**.
3) Help to maintain the shape of skeletal system.

### 3. Keratan sulfate:

a) **Structure**: The repeated disaccharide unit consists of:

1) Galactose (no uronic acid), with sulfate on $C_6$.
2) N-acetylglucosamine with sulfate on $C_6$.

b) **Site:**

1) Cornea. 2) Cartilage.

c) **Functions:**

It plays an important role in corneal transparency.

### 4. Dermatan sulfate:

a) **Structure:** The repeated disaccharide unit consists of:

1) L-Induronic acid.
2) N-acetylgalactosamine with sulfate on $C_6$.

b) **Site:**

1) Cornea. 2) Sclera.
3) Skin, blood vessels and heart valves.

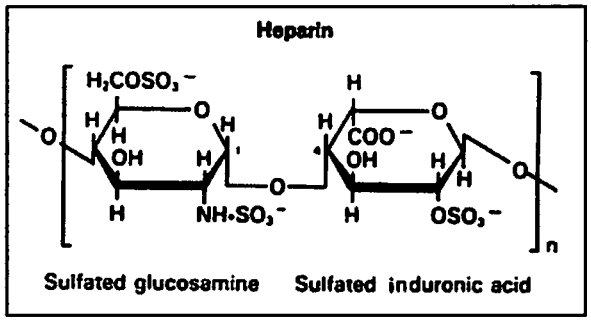
c) **Functions:**

1) **In cornea**, it plays-together with keratan sulfate, an important role in corneal transparency.
2) **Its presence in sclera** may play a role in maintaining the overall shape of the eye.

### 5. Heparin:

a) **Structure:** The repeated disaccharide unit consists of:

1) Induronic acid with sulfate on $C_2$.
2) Glucosamine with sulfate on $C_2$ and $C_6$.




b) **Site:** Heparin present in mast cells (intracellular compound). Mast cells are located along the wall of blood vessels of liver, lungs, skin, heart, kidney and spleen.

c) **Functions:**

1) It acts as **anticoagulant.**

2) **Heparan sulfate** ( *which has the same structure as heparin except some glucosamines are acetylated and there are fewer sulfate groups),* has the following functions:

- ➢ It acts as cell membrane receptors.
- ➢ It participates in cell adhesion and cell-cell interaction.
- ➢ It is present in basement membrane of the kidney and plays a role in the glomerular filtration.

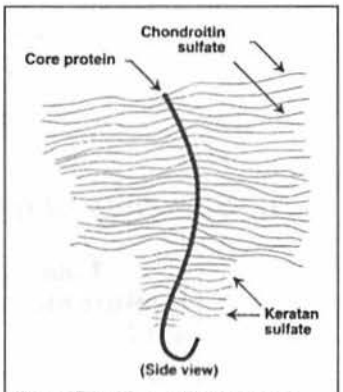
## II. *Summary of glycosaminoglycans:*

| Type | Structure | Site | Functions |
|---|---|---|---|
| **Hyaluronic acid** | Glucuronic acid | Cartilage | lubricant in joints |
| | N-acetylglucosamine | Connective tissue | makes cartilage compressible |
| | | Synovial fluid | cell migration during wound repair |
| | | Vitreous body of the eye | cell migration during morphogenesis |
| **Chondroitin 4 – and 6 sulfate** | Glucuronic acid | Cartilage, tendons, ligaments and bones | In cartilage: it binds collagen and hold fibers in strong network |
| | N-acetylgalactosamine with sulfate on either $C_4$ or $C_6$. | Aorta, skin, cornea, umbilical cord and in certain neurons | maintain the shape of skeletal system |
| **Keratan sulfate** | Galactose (no uronic acid), with sulfate on $C_6$ | Cornea | corneal transparency |
| | N-acetylglucosamine with sulfate on $C_6$ | It is found as proteoglycan in cartilage | |
| **Dramatan sulfate** | L-Induronic acid | Cornea | corneal transparency |
| | N-acetylgalactosamine with sulfate on $C_6$ | Sclera, Skin, blood vessels and heart valves | overall shape of the eye |
| **Heparin** | Induronic acid with sulfate on C2 | mast cells | anticoagulant |
| | Glucosamine with sulfate on $C_2$and $C_6$ | | Heparan sulfate has the following functions: |
| | | | acts as cell receptors |
| | | | Cell adhesion and cell-cell interaction |
| | | | It is present in basement membrane of the kidney |

# *Conjugated Carbohydrate*

**They include:**

1- **Glycolipids:** see lipids chemistry.
2- **proteoglycans and Glycoproteins.**
3- **Fibronectin.**
4- **Laminin.**



Example of proteoglycans.

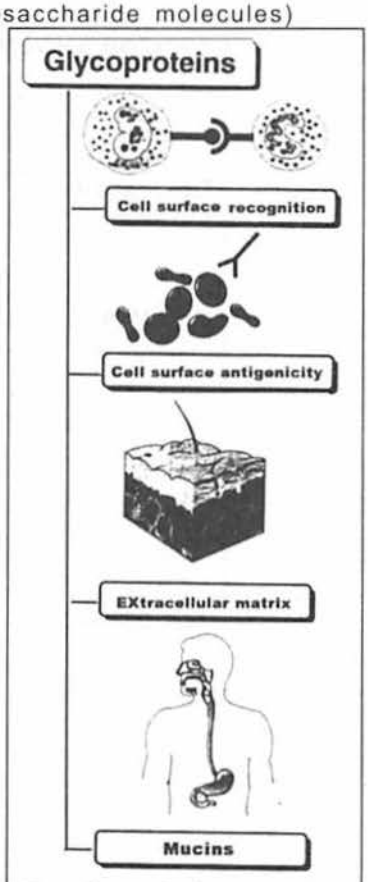
**I. *Proteoglycans and Glycoproteins:*** Proteoglycans and glycoproteins are proteins containing carbohydrates. They differ from each other in that they are present in different sites, contain different sugars and have different shape and size.

A. **Proteoglycans**:

These are chains of glycosaminoglycans attached to protein molecule e.g. hyaluronic acid, chondroitin sulfate, keratan sulfate, dermatan sulfate, heparin and heparan sulfate. They serve as a ground substance and associated with structure elements of tissues as bone, elastin and cartilage (see functions of glycosaminoglycans). The carbohydrate part is presented in very long unbranched chains (more than 50 monosaccharide molecules) attached to protein core.

B. **Glycoproteins (mucoproteins)**:

1. **Structure:** They consists of:
   a) **Protein core.**
   b) **Carbohydrate chains** which are branched short chain( from 2-15 monosaccharide units) such chains are usually called oligosaccharide chains. They include:
      1) **Hexoses:** Galactose and mannose.
      2) **Acetylhexosamines**: N-acetylglucosamine.
      3) **Pentoses:** Arabinoe and xylose.
      4) **Methylpentose:** L-fucose.
      5) **Sialic acid.**
      6) They contain no uronic acids or sulfate groups.
2. **Functions:**
   a) Glycoproteins are components of **extracellular matrix**.



Functions of glycoproteins

b) They are components of **mucins** of gastrointestinal and urogental tracts, where they act as protective biologic lubricants.

c) **Glycoproteins are components of cell membrane as:**

1) **Blood group** antigens (A, B, AB).
2) **Cell surface receptors**: e.g. for hormones.
3) **Glycophorin**: It is glycoprotein present in human red cell membrane. It prolonged the life span of the lipid membrane.

d) **Plasma proteins**: present in plasma are glycoproteins.

e) Most **enzymes** and **protein hormones** glycoproteins

**Differences between glycoproteins and proteoglycans :**

| | Glycoproteins | Proteoglycans |
|---|---|---|
| 1. **Structure:** ▪ **Carbohydrate component:** | Oligosaccharide units | Glycosaminoglycans |
| • **Types of sugar:** | Contain no uronic acid | Contain uronic |
| | **Pentoses:** as arabinose and xylose. | Sugaramines as glucosamines. |
| | **Methylpentoses:** L-fucose | |
| • **Sulfate group:** | Contain no sulfate | Contain sulfate. |
| • **Size of carbohydrate component:** | 2 – 15 units. | More than 50 units. |
| • **Repeating structure:** | Little or non. | Repeating disaccharides. |
| • **Shape:** | Usually branched | Linear, unbranched. |
| 2. **Functions:** | • Extracellular matrix<br>• Mucin.<br>• Blood group antigens e.g. A, B and AB.<br>• Cell receptors.<br>• Glycophorins.<br>• Plasma proteins.<br>• Some hormones.<br>• Enzymes.<br>• Antibodies. | • Ground substances and supporting tissues as cartilage, bones and tendons.<br>• Cell membrane. |

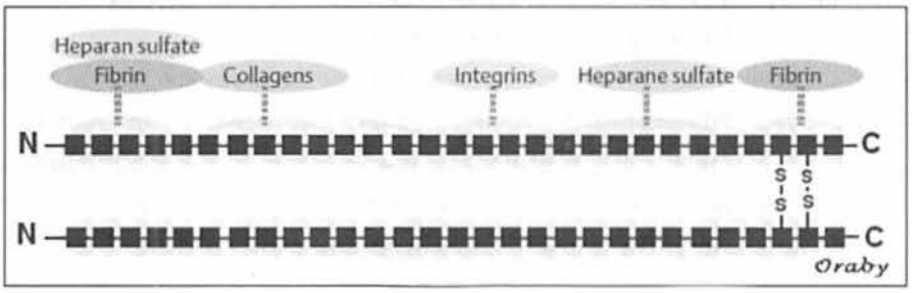
## II. *Fibronectin:*

A. **Structure:**

1. It is a high-molecular weight (~440kDa) extracellular matrix glycoprotein.
2. Fibronectin exists as a dimer, consisting of two nearly identical monomers linked by a pair of disulfide bonds.
3. Two types of fibronectin are present:

a) **Soluble plasma fibronectin.** It is produced in the liver by hepatocytes.

b) **Insoluble cellular fibronectin** is a major component of the extracellular matrix. It is secreted by various cells, primarily fibroblasts.




B. **Functions:**

Fibronectin plays a major role in cell adhesion, growth, migration and differentiation, and it is important for wound healing and embryonic development.

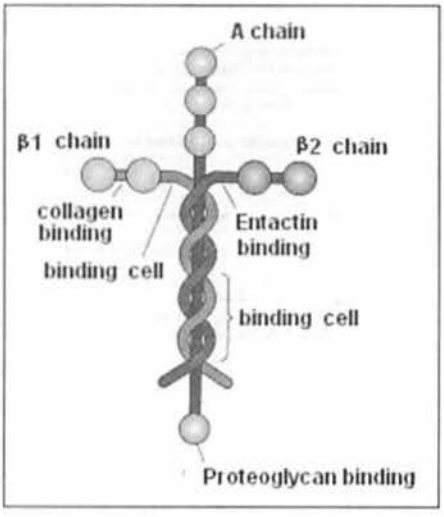
NOTE:

- Fibronectin binds to membrane receptor proteins called integrins.
- In addition to integrins, fibronectin also binds extracellular matrix components such as collagen, fibrin and heparan sulfate proteoglycans.

## III. *Laminin:*

A. **Structure:**

1. **Laminin** (about 850 kDa, 70 nm long) consists of three distinct elongated polypeptide chains (A, B1, and B2). It has binding sites for:
   a) Proteoglycans.
   b) Collagen.
   c) **Entactin,** the major cell attachment factor.
2. It has four arms that can bind to four other molecules. The three shorter arms are particularly good at binding to other laminin molecules. The long arm is capable of binding to cells, which helps anchor the actual organs to the membrane.




B. **Function:**

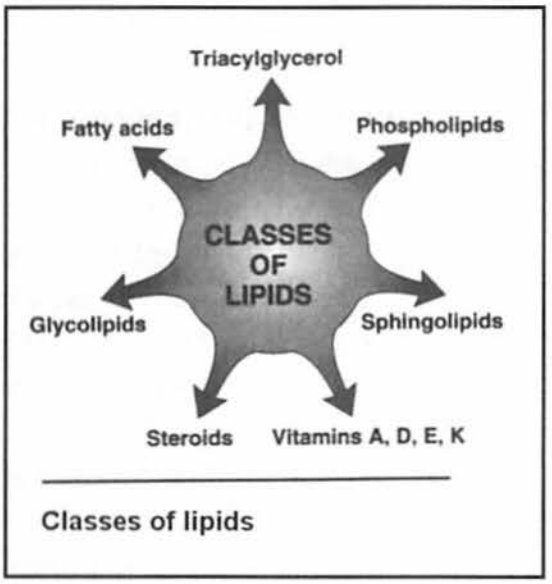
1. Laminin is a glycoprotein found in the extracellular matrix.
2. It forms the basement membrane of all internal organs i.e. the major component on which epithelium cells sit.
3. Laminin is vital to making sure that the overall body structures are hold together.

C. **Laminin found in the renal glomerulus:**

1. Laminin is a major protein component of renal glomerulus. It is one component of basal laminas.
2. The primary components of the basal lamina are four proteins—laminin, collagen, entactin, and proteoglycans.
3. The relatively thick basal lamina of the renal glomerulus has an important role in **glomerular filtration.**

# Chapter 2 *Lipids Chemistry*

## I. *Introduction to lipids:*



Classes of lipids

**A. Definitions:**

1. Lipids are a heterogeneous group of compound related to fatty acids.
2. Lipids are relatively **insoluble in water.**
3. They are **soluble in nonpolar solvents** such as ether, chloroform or benzene.

**B.** The hydrophobic (water-hating) nature of lipids is due to the predominance of hydrocarbon chains ($-CH_2-CH_2-CH_2-$) in their structure.

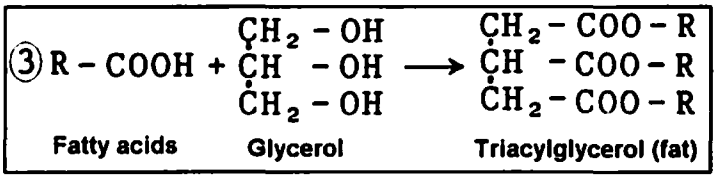
**C. Classification:** lipids are classified into simple, complex (compound) and derived lipids:

**Classification of lipids**

| Simple | Compound | Derived |
|---|---|---|
| Fats (acylglycerols) (Glycerol + FAs) | Phospholipids: Glycerophospholipids, Sphingophospholipids | Fatty acids |
| Waxes (Higher alcohol + FA) | Glycolipids: Cerbrosides, Gangliosides, Ceramide oligosaccharides | Steroids |
| | Lipoproteins: Chylomicrones, VLDL, LDL, HDL | Fat soluble vitamins |
| | | Ketone bodies |
| | | Carotenoids |
| | | cholanthrenes |

1. **Simple lipids:** are esters of fatty acids with various alcohols. (Ester bond = **-COO-**). They are either fats or waxes.

*a)* **Fats:** are esters of fatty acids with glycerol (Acylglycerols).




*b)* **Waxes:** are esters of fatty acids with higher alcohols.

2. **Complex (compound) lipids:** are esters of fatty acids with alcohol in addition to other groups. They include :
   *a)* **Phospholipids:** They contain phosphate. They include:
      1) **Glycerophospholipids:** the alcohol is **glycerol.**
      2) **Sphingophospholipids:** the alcohol is **sphingosine.**
   *b)* **Glycolipids** : They contain carbohydrate:
   *c)* **Lipoproteins:** They consist of lipids conjugated with proteins.

3. **Derived and precursor lipids** :which include :
   *a)* Substances which are given by hydrolysis of simple and complex lipids e.g. fatty acids and alcohols.
   *b)* Substances which are insoluble in water but soluble in nonpolar solvents as :
      1) Steroids.
      2) Carotenoids.
      3) Cholanthrenes.
      4) Ketone bodies.
      5) Fat soluble vitamins

## D. <u>Functions (biomedical importance)</u>:

1. **In diet** : Lipids are important constituent of diet due to:
   *a)* They are a source of high energy value.
   *b)* They contain fat soluble vitamins.
   *c)* They contain essential fatty acids.
   *d)* They make diet palatable.
2. **In the body** :
   *a)* Lipids in adipose tissue serve as storage form of energy.
   *b)* They serve as **thermal insulator** in the subcutaneous tissues.
   *c)* Nonpolar lipids act as **electrical insulator,** allowing rapid propagation of waves along myelinated nerves.
   *d)* **Lipoproteins** (a combination of fat and proteins) are important because :
      1) They enter in the structure of cell membranes.
      2) They serve as a transport form of energy in the blood.

**E. Neutral lipids:** are those which carry **no** charges and include:

1. Neutral fats (acylglycerols).
2. Cholesterol and cholesteryl esters.

# *Chemistry of Fatty Acids, Alcohols and Simple Lipids*

## ***Fatty acids:*** *R.COOH*

### *I.* ***Introduction:***

**A.** Fatty acids are **water-insoluble** long chain hydrocarbons.

**B.** Fatty acids may be **saturated** (containing no double bonds) or **unsaturated** (containing one or more double bonds).

**C.** They are mostly **monocarboxylic** i.e. having one carboxyl group at the end of the chain (-COOH).

**D.** They are mostly **aliphatic** (i.e. not branched). A few branched chain fatty acids are present in animals and plants.

**E.** Fatty acids occur mainly as **esters** in natural fats and oils.

**F.** Fatty acids may also present as **free fatty acids** in the plasma.

### *II.* ***Saturated fatty acids :***

**A.** Have no double bonds in the chain.

**B.** Their general formula is **$CH_3$-$(CH_2)_n$-COOH** where (n) equals the number of methylene (-$CH_2$) groups between the methyl and carboxylic groups.

**C.** The systemic name of saturated fatty acids ends by the suffix **(-anoic)** e.g. palmitic acid (16C) has systemic name **hexadecanoic** acid (Hexa =6, Deca =10).

Saturated fatty acids.

| Common Name | Number of C Atoms | Occurance |
|---|---|---|
| Formic[1] | 1 | Takes part in the metabolism of "$C_1$" units (formate) |
| Acetic | 2 | Major end product of carbohydrate fermentation by rumen organisms[2] |
| Propionic | 3 | An end product of carbohydrate fermentation by rumen organisms[2] |
| Butyric | 4 | In certain fats in small amounts (especially butter). An end product of carbohydrate fermentation by rumen organisms[2] |
| Valeric | 5 | |
| Caproic | 6 | |
| Caprylic (octanoic) | 8 | In small amounts in many fats (including butter), especially those of plant origin |
| Capric (decanoic) | 10 | |
| Lauric | 12 | Spermaceti, cinnamon, palm kernel, coconut oils, laurels |
| Myristic | 14 | Nutmeg, palm kernel, coconut oils, myrtles |
| Palmitic | 16 | Common in all animal and plant fats |
| Stearic | 18 | |
| Arachidic | 20 | Peanut (arachis) oil |
| Behenic | 22 | Seeds |
| Lignoceric | 24 | Cerebrosides, peanut oil |

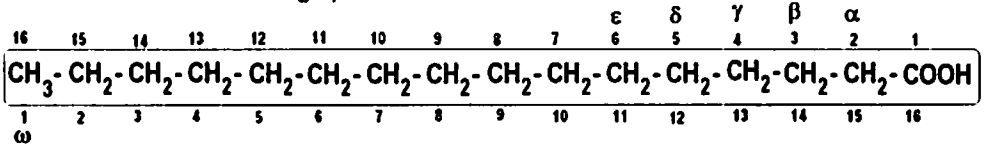
[1]Strictly, not an alkyl derivative.
[2]Also in the colon of humans.

**D. <u>Example of the formula of some saturated fatty acids</u>:**

1. Butyric acid (4C) = $CH_3$ - $CH_2$ - $CH_2$ -COOH.

2. Caproic acid (6C) = $CH_3 - CH_2 - CH_2 - CH_2 - CH_2 - COOH$.
3. Palmitic acid (16C) = $CH_3 - (CH_2)_{14} - COOH$.
4. Stearic acid (18C) = $CH_3 - (CH_2)_{16} - COOH$.

**E. <u>Numbering of carbon atoms</u>:** Many methods are used to number the carbon atoms e.g. palmitic acid.




1. **Counting starting from carboxylic (-COOH) group** = carbon No.1 is that of carboxylic group, carbon No. 2 is the carbon adjacent to the carboxyl carbon and so on.
2. **Counting from carbon adjacent to carboxyl carbon** i.e. carbon No.2: carbons may be numbered as α , β , γ and so on.
3. **Counting from last methyl carbon** ($CH_3$) which is called omega carbon (ω). The carbon adjacent to it is carbon No.2 and so on.

## *III. Unsaturated fatty acids :*

**A.** The general formula is **$C_n - H_{2n-1} - COOH$.**

**B.** The systemic name of unsaturated fatty acids ends by the suffix **(-enoic)** e.g. oleic acid (18 carbons) has systemic name **octadecenoic** acids (Octa = 8 , Deca = 10).

**System of numbering and position of double bonds**

**a- Numbering of carbon atoms:** same as in saturated fatty acids.

**b- Position of double bonds:** The most commonly used systems for designating the position of double bonds in unsaturated fatty acids are:

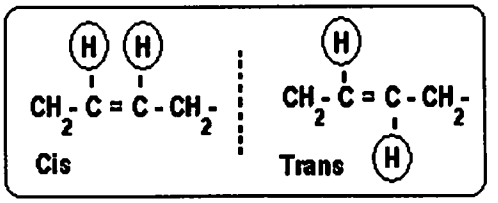
**(1) The delta (Δ) numbering system** e.g. palmitoleic acid , C 16 : 1 $\Delta^9$ means that this acid contains 16 carbons (16) and one double bond (1) and the position of double bond is between carbon number 9 and carbon number 10 starting from carboxyl carbon 1.

**(2) Omega (ω) system** e.g. the palmitoleic acid may be written as: C 16:1 ,ω7 which indicates a double bond on seventh carbon counting from the ω-carbon atom i.e. last **-$CH_3$ carbon.**

**Cis and trans double bonds:** Double bonds in naturally occurring fatty acids in mammals are always in a cis form (configuration) not as trans form: polyunsaturated acids:

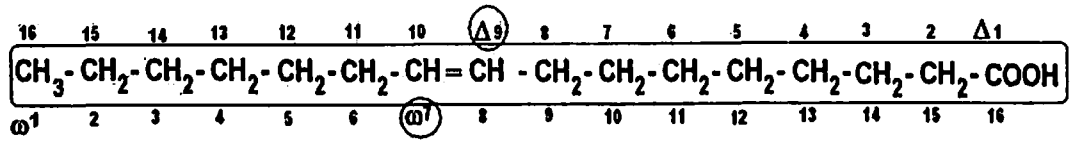
a) **Cis** form means that the groups are on the same side.

b) **Trans** form means that the groups are on the opposite sides. Tans fatty acid may be present in certain foods, during hydrogenation of oils to manufacture margarine.



C. Unsaturated fatty acids are either monounsaturated or polyunsaturated acids:

1. **Monounsaturated (monothenoic, monoenoic) fatty acids i.e.** contain one double bond e.g. palmitoleic (16:1 $\Delta^9$ ) and oleic acid (18:1 $\Delta^9$).




**Palmitoleic acid (*C* 16:1 $\Delta^9$) = (*C* 16:1 $\omega^7$)**

**Unsaturated fatty acids**

| Number of *C* atoms and number and position of double bonds | Series | Common name | Systemic name | Occurance |
|---|---|---|---|---|
| **Monounsaturated fatty acids** | | | | |
| 16:1;9 | ω7 | Palmitoleic | *cis*-9-Hexadecenoic | In nearly all fats. |
| 18:1;9 | ω9 | Oleic | *cis*-9-Octadecenoic | Possibly the most common fatty acid in natural fats. |
| 18:1;9 | ω9 | Elaidic | *trans*-9-Octadecenoic | Hydrogenated and ruminant fats. |
| 22:1;13 | ω9 | Erucic | *cis*-13-Docosenoic | Rape and mustard seed oils. |
| 24:1;15 | ω9 | Nervonic | *cis*-15-Tetracosenoic | In cerebrosides. |
| **Polyunsaturated fatty acids (2 double bonds)** | | | | |
| 18:2;9,12 | ω6 | Linoleic | all-*cis*-9,12-Octadecadienoic | Corn, peanut, cottonseed, soybean, and many plant oils. |
| **Polyunsaturated fatty acids (3 double bonds)** | | | | |
| 18:3;6,9,12 | ω6 | γ-Linolenic | all-*cis*-6,9,12-Octadecatrienoic | Some plants, eg, oil of evening primrose; minor fatty acid in animals. |
| 18:3;9,12,15 | ω3 | α-Linolenic | all-*cis*-9,12,15-Octadecatrienoic | Frequently found with linoleic acid but particularly in linseed oil |
| **Polyunsaturated fatty acids (4 double bonds)** | | | | |
| 20:4;5,8,11,14 | ω6 | Arachidonic | all-*cis*-5,8,11,14-Eicosatetraenoic | Found with linoleic acid particularly in peanut oil; important component of phospholipids in animals. |
| **Polyunsaturated fatty acids (5 double bonds)** | | | | |
| 20:5;5,8,11,14,17 | ω3 | Timnodonic | all-*cis*-5,8,11,14,17-Eicosapentaenoic | Important component of fish oils, eg, cod liver oil. |
| 22:5;7,10,13,16,19 | ω3 | Clupanodonic | all-*cis*-7,10,13,16,19-Docosapentaenoic | Fish oils, phospholipids in brain. |
| **Polyunsaturated fatty acids (6 double bonds)** | | | | |
| 22:6;4,7,10,13,16,19 | ω3 | Cervonic | all-*cis*-4,7,10,13,16,19-Docosahexaenoic | Fish oils, phospholipids in brain. |

2. **Polyunsaturated fatty acids (essential fatty acids, =polyethenoic, =polyenoic fatty acids):** Containing more than one double bond: e.g

*a)* **Linoleic (18:2 $\Delta^{9,12}$, $\omega^6$) and lenolenic (18:3 $\Delta^{9,12,15}$, $\omega^3$):**

1) They are present in linseed oil.

*b)* **Arachidonic acid (20:4 $\Delta^{5,8,11,14}$, $\omega^6$):**

1) It is present in peanut oil.

2) It is a precursor of eicosanoids (see later).

3) It is a component of phospholipids in animals.

*c)* **Clupanodonic acid: (22:5 $\Delta^{7,10,,13,16,19}$, $\omega^3$):**

1) It is present in fish oils.

2) It is a component of phospholipids in brain.

*IV.* ***Branched-chain fatty acids:*** Almost all fatty acids present in mammalian tissues are aliphatic i.e. straight chain. However, branched-chain fatty acids are found in nature.

**A.** **phytanic acid (18C)**: Some milk products contain branched chain fatty acid called phytanic acid (18C). It contains 4 methyl groups at position 3, 7, 11 and 15 carbons.

**B.** **Refsum's disease**:

1. It is caused by inability of oxidation of phytanic acid. This leads to its accumulation in plasma and tissues.
2. **Manifestations:** nervous tissue damage in the form of blindness and deafness.

## *V.* *Essential and nonessential fatty acids:*

**A.** **Nonessential fatty acids**:

1. These are fatty acids which **can be synthesized** in the body. Thus they are not necessary to be obtained from the diet.
2. They include all saturated and monounsaturated (one double bond) fatty acids as palmitoleic and oleic acid.
3. They can be synthesized from **acetyl CoA** (active acetate) derived from glucose oxidation.

**B.** **Essential fatty acids**:

1. **Definition:**

*a)* These are fatty acids that **cannot be synthesized** in the body. They must be obtained from the diet.

*b)* They include fatty acids that contain more than one double bond **(polyunsaturated fatty acids)**, e.g. lenoleic, lenolenic and arachidonic acids.

*c)* **A type of essential fatty acids are ω-3 fatty acids (omega-3 fatty acids)** which are a family of unsaturated fatty acids that have double bond in the ω -3 position; that is, the third bond from the methyl end of the fatty acid. Examples of *ω -3* fatty acids include linolenic acid and arachidonic acids.

*d)* The human body has enzyme system that can **form only** one double bond at the ninth carbon atom ($\Delta^9$).

2. **Sources:**

*a)* **Plant oils** e.g. corn oil, soya bean oil, safflower oils, sunflower, linseed oil and cotton seed oil.

*b)* **Fish oils**: shark liver oils, which particularly contain the $\omega^3$ polyunsaturated fatty acids.

3. **Importance (functions):** Essential fatty acids are important for:
   *a)* Normal growth.
   *b)* They enter in the structure of phospholipids and cholesterol esters.
   *c)* They enter in the structure of cell membranes and are required for the fluidity of membrane structure.
   *d)* They protect against atherosclerosis and coronary heart disease by decreasing free cholesterol and LDL.
   *e)* **Arachidonic acid (20C)** is a precursor of a group of compounds called: **eicosanoids.**

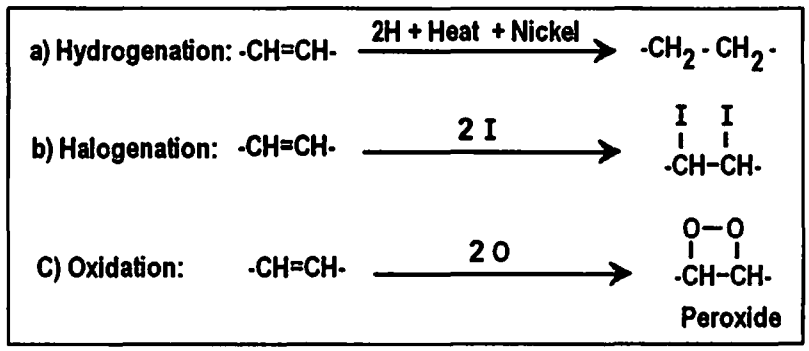
## *VI.* ***Properties of fatty acids:***

### A. Physical properties:

1. **Solubility :**
   *a)* Short chain fatty acids e.g. acetic (2C), butyric (4C) and caproic (6C) are soluble in water.
   *b)* Long chain fatty acids are insoluble in water but soluble in nonpolar fat solvents.
2. **Melting point :** It depends on the length of the chain of fatty acids and the degree of unsaturation, so :
   *a)* Short chain and unsaturated fatty acids are liquid at room temperature.
   *b)* Long chain saturated fatty acids are solid at room temperature.

### B. Chemical properties:

1. **Hydrogenation, halogenation and oxidation:** These are




2. **Salt formation (soap):** Fatty acids form soap (salts) with alkalies as NaOH, KOH, $Ca(OH)_2$:

**R.COOH + NaOH → R.COONa + $H_2O$**

**Fatty acid Sodium hydroxide Sodium salt**

3. **Ester formation:**
   *a)* Fatty acids form **esters (R.COO.R)** with alcohols:

$$R.COOH + R_1.OH \text{ ----▶ } R.COOR_1 + H_2O$$

   1) Esters of fatty acids with glycerol ----▶ Neutral fats (Acylglycerols).
   2) Esters of fatty acids with higher alcohols ----▶ waxes

## *VII.* ***Eicosanoids:***

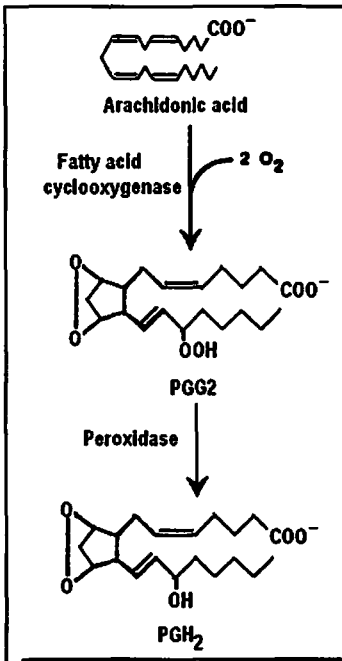
**Prostanoids:**
- Prostaglandins.
- Prostacyclines.
- Thromboxanes.

**Leukotriens (LT).**

**A. Definition:** These are cyclic compounds that derived from arachidonic acid (eicosatetraenoic) (20 C) after cyclization of its carbons chain to form a ring.

**B. Components of eicosanoids:**

1. **Prostanoids:** which comprise prostaglandins, prostacyclins and thromboxanes:
   *a)* **Prostaglandins (PG):**
      1) (A, B, D, E, F, H, G and I).
      2) They have hormonal like action.
      3) They cause vasodilatation, contraction of the uterus and intestine.
   *b)* **Prostacyclines:** They cause vasodilatation and inhibit platelets aggregation.
   *c)* **Thromboxanes:** They cause aggregation of platelets.
2. **Leukotriens (LT):**
   *a)* They are present in leucocytes, platelets and mast cells.
   *b)* They cause chemotaxis i.e. Collection of white blood cells at the site of inflammation.

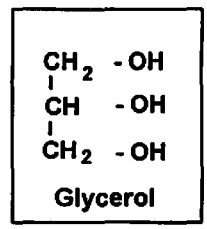



Oxidation and cyclization of arachidonic acid

## ***Alcohols:*** *R.OH*

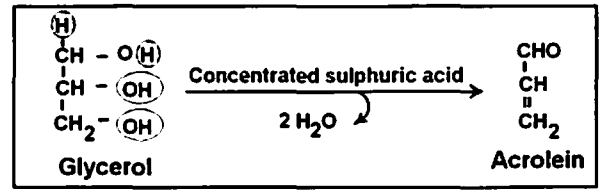
*I.* ***Introduction:*** Alcohols associated with lipids include **glycerol, cholesterol** and **higher alcohols** (e.g. cetyl alcohol, $C_{16}H_{33}OH$) usually found in the wax.

*II.* ***Glycerol:*** It is polyhydric alcohol containing 3 (-OH) groups:



A. **Properties:**

1. Glycerol is colorless, odorless, hygroscopic and has sweet taste.
2. It is **soluble in water** and alcohol, insoluble in nonpolar solvents.
3. It combines with one fatty acid to form **monoacylglycerol**, two fatty acids to form diacylglycerols and three fatty acids to form triacylglycerols. This combination is through ester linkage.
4. **Acrolein:** It is an aldehyde substance with a characteristic odour. It derives from glycerol by losing 2 water molecules.



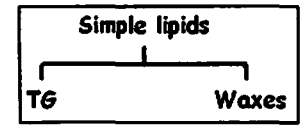

B. **Uses of glycerol:**

1. Nitroglycerol is used - as a drug - for dilatation of coronary artery.
2. Glycerol enters in manufacturing of creams and lotions for dry skin.

*III.* **Cholesterol:** is an alcohol and derived lipids (see later).

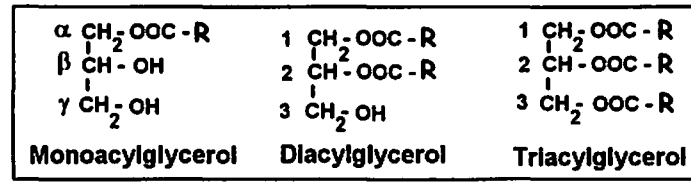
*IV.* **Higher alcohol:** They contain one (-OH) group i.e. monohydric alcohols.

## *Simple lipids*




### *I. Introduction:*

A. *They are called simple because they are formed only from alcohols and Fatty acids. There are two classes of simple lipids (according to the type of alcohol): acylglycerols and waxes. Acylglycerols are esters of one, two or three fatty acids with glycerol.*




B. ***Numbering of carbons of glycerol** is either: α, β and γ or 1, 2 and 3. **Notice that** carbon 1 and 3 of glycerol in triacylglycerols are **not identical** when viewed in 3 dimensions. Enzymes can differentiate between the two positions.*

### *II. Triacylglycerols (triglycerides):*

A. They are called **neutral fat** because they carry no charge.

B. **Body triacylglycerols:**

1. **Location**: They are stored mainly in **cytoplasm of adipose tissue cells** (which is located subcutaneously and around kidney and other organs).

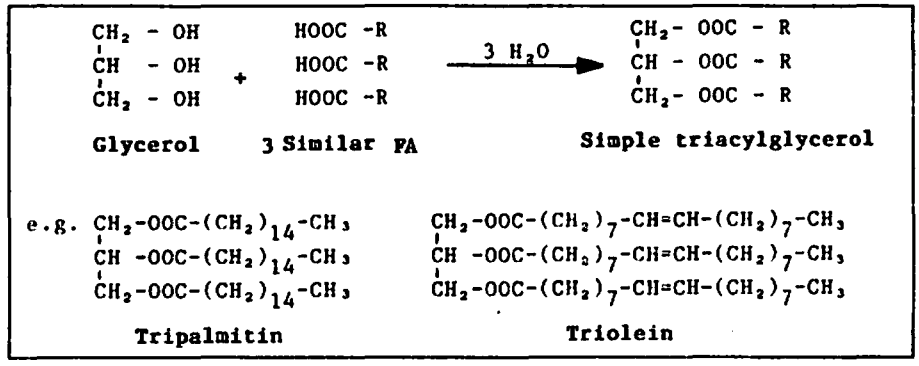
2. Body fat is important source of energy. Each gram fat gives 9.3 kcal.
3. Human fat is liquid at room temperature and contains high contents of oleic acid.

## C. Dietary sources of triacylglycerols:

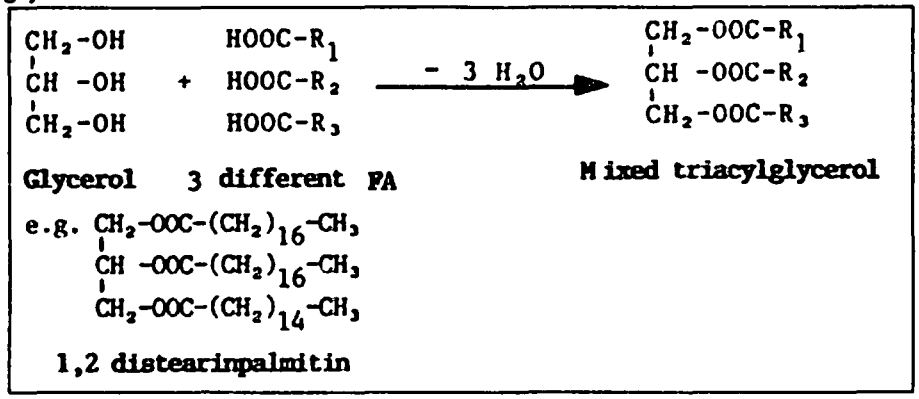
1. **In animals** e.g. butter and lards.
2. **In plants** e.g. cotton seed oil, linseed oil, sesame oil and olive oil.
3. **Marine oils** e.g. cod liver oil and shark liver oil.

## D. Types of triacylglycerols: simple or mixed.

1. **Simple triacylglycerols:** similar 3 fatty acids are attached to glycerol.




2. **Mixed triacylglycerols:** 3 different fatty acids are attached to glycerol.




## E. Properties of triacylglycerols:

1. **Physical properties:**
   - *a)* **Solubility:** All triacylglycerols are insoluble in water, soluble in fat solvents.
   - *b)* **Melting point:**
     1) Triacylglycerols rich in unsaturated fatty acids are liquid at room temperature. They are called oils.

2) Triacylglycerols rich in saturated fatty acids are solid at room temperature. They are called fats.

*c)* **Specific gravity:** It is less than one. Specific gravity of water is one. Therefore, triacylglycerols float on the surface of water.

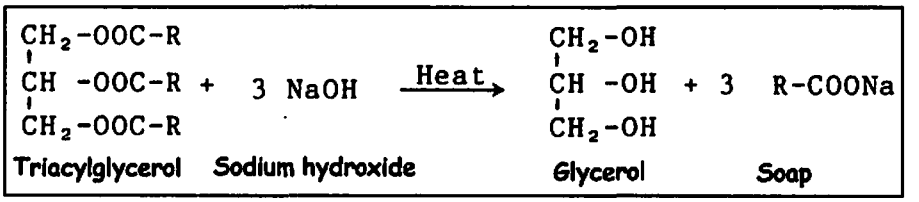
*d)* **Grease stain test:** All Triacylglycerols give positive grease stain test.

**2. Chemical properties:**

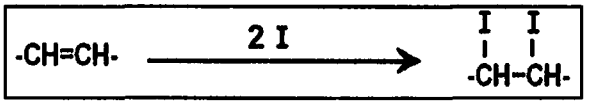
*a)* **Acroline test:** All triacylglycerols contain glycerol. So all give positive acroline test.

*b)* **Hydrolysis: Lipase enzymes** present in digestive and other systems can hydrolyze triacylglycerols into fatty acids and glycerol. (Note: hydrolysis means breakdown of substance by addition of water).

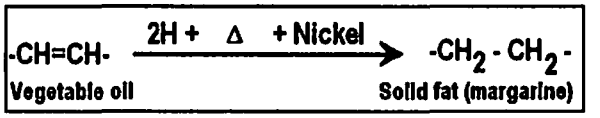
*c)* **Saponification:** Alkalies as NaOH and KOH can react with triacylglycerols breaking them into glycerol and salts of fatty acids. These salts are called **soaps** and the process is called: **saponification.** Soaps cause emulsification of oily material (i.e. breaking down large fat particles into small ones). This helps easy washing the fatty materials away.




*d)* **Halogination:** This depends on the presence of unsaturated fatty acids in the triacylglycerol molecules.



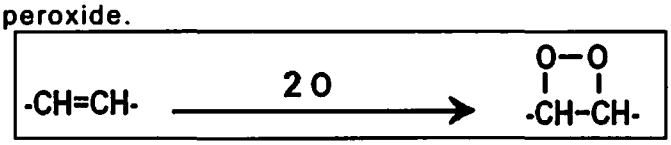

*e)* **Hydrogenation:** This also depends on the presence of unsaturated fatty acids in the molecules. Hydrogen is usually added at high temperature in the presence of nickel as a catalyst. This reaction is the base of conversion of oils into margarine (Harding of oils).



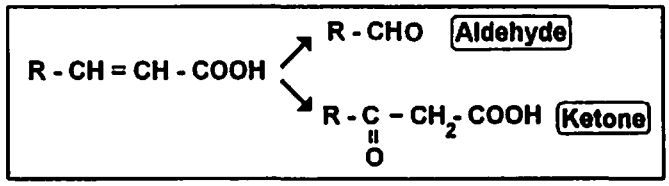

*f)* **Oxidation = Rancidity** (see later).

## F. Rancidity:

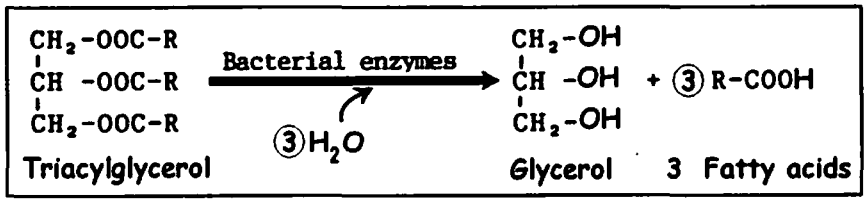
1. **Definition:** It is a toxic reaction of triacylglycerols. It is due to oxidation of its unsaturated fatty acids content by oxygen of the air, bacteria or moisture. It leads to unpleasant odor or taste of oils and fats.
2. **Types of rancidity:**
   a. **Oxidative rancidity:** Fatty acids are oxidized at double bonds giving peroxide.




   b. **Ketonic rancidity:** produces aldehyde and ketone with characteristic taste:




   c. **Hydrolytic rancidity:** triacylglycerols are hydrolyzed by bacterial enzymes into glycerol and fatty acids. The free fatty acids can then undergo further auto-oxidation with a free radicals.




3. **Enhancement of rancidity:** This can be done by certain substances as:
   *a)* Free radicals as reactive oxygen species.
   *b)* Lead or copper.
   *c)* Heme compounds.
   *d)* The enzyme: lipooxygenase found in platelets.
   **Note:** See free radicals and antioxidants (part I).
4. **Detection of rancidity:** By copper acetate test that detects the free hydrolyzed fatty acids.
5. **Prevention of rancidity:** The addition of antioxidant delays or prevents the process of rancidity. **Examples of antioxidants are:**
   *a)* **Vitamins:** as vitamins E and C.
   *b)* Substances containing **-SH group**, e.g. cysteine amino acid.
   *c)* Avoidance of oxygen of the air, bacteria or moisture.

*III.* **Waxes:** These are esters of fatty acids with long chain alcohol other than glycerol. These alcohols contain one (-OH) group, i.e., monohydric alcohols e.g. bee wax.

A. **Sources:** Waxes are excreted extracellularly in some plants and animals and has a protective function as in:

1. Bee wax.
2. Sebaceous secretions.
3. Cuticles of leaves.

B. **Properties:**

1. They have the same physical properties as fat.
2. They give negative acrolein test because they contain no glycerol.
3. They are not digested by lipase enzyme. Thus they are not utilized by the body.
4. They are solids at room temperature.

**Differences between triacylglycerols and waxes:**

| | *Triacylglycerols* | *Waxes* |
|---|---|---|
| ***Composition*** | Contain glycerol i.e. give **positive acrolein** test. | Contain no glycerol so, give **negative acrolein** test. |
| ***Melting point*** | At room temperature: they are either **solids or liquids.** | At room temperature, they are **solids.** |
| ***Rancidity*** | They may undergo rancidity. | They do not undergo rancidity. |

# *Complex (compound) lipids*

I. ***Introduction:*** These include phospholipids, glycolipids, lipoproteins, sulpholipids and aminolipids.

A. **Phospholipids:** They contain **phosphoric acid residues.** They are classified into **glycerophospholipids** (contain glycerol) and **sphingophospholipids** (contain sphingosine). Phospholipids include:

1. **Phosphatidic acid (diacylglycerolphosphate):**
   *a)* **Structure:** Glycerol + Saturated fatty acid (attached to 1 (α) position, Unsaturated fatty acid (attached to 2 (β) position + phosphoric acid residue at position 3(γ).
   *b)* **Function:** It has no function. It is produced as an intermediate in the synthesis of triacylglycerols and phospholipids.

2. **Cardiolipin (diphosphatidylglycerol):**
   *a)* **Structure:** It is formed of two phosphatidic acids linked together by glycerol.
   *b)* **Function:**
      1) Cardiolipin is the major lipid in mitochondrial membrane.
      2) It stimulates antibody formation i.e. antigenic.

3. **Lecithin (phosphatidyl choline):**
   *a)* **Structure:**
      1) Glycerol.
      2) Saturated fatty acid (attached to 1 (α) position.
      3) Unsaturated fatty acid (attached to 2 (β) position.
      4) Phosphoric acid (attached to 3(γ) position.
      5) Choline base (attached to phosphoric acid).
   *b)* **Functions:**
      1) **Lecithin enters in the structure of cell membrane.** It is the most abundant phospholipid in cell membrane.
      2) **Lecithin acts as lipotropic factor** i.e. prevent accumulation of fat in liver (fatty liver).
      3) **Lecithin forms cholesterol esters:** Lecithin reacts with cholesterol, giving cholesterol ester and lyso-lecithin in the presence of LCAT enzyme (lecithin cholesterol acyl transferase). Cholesterol esters is transported to the liver and excreted with bile. This prevents atherosclerosis.

**Lecithin + Cholesterol** $\xrightarrow{LCAT}$ **Cholesterol ester + lysolecithin**

      4) Lecithin acts as body **store of choline**. Choline is important for:
         i- **Nerve transmission.**
         ii- **Transmethylation:** It acts as *methyl donor* in transmethylation reaction.
      5) **Lecithin prevents gall stones:** lecithin in bile solubilizes cholesterol and prevent cholesterol stones in gall bladder
      6) **Dipalmityl lecithin** (i.e. lecithin which contains 2 palmitic acid residues) acts as **a surfactant in the lung.**
         i- Dipalmityl lecithin is continuously secreted by the lung cells in the alveolar wall, forming a monolayer over the watery surface of the alveolus and so **lowers the surface tension.** This helps expiration and inspiration.
            - **During expiration,** the surfactant becomes solid under pressure. This prevents the adherence of alveolar wall.

- **During inspiration,** The surfactant makes the lung easier to expand.

ii- **Respiratory distress syndrome (hyaline membrane disease):**

- In premature babies, lungs do not secrete enough surfactant. This leads to **lung collapse** and death from ***respiratory failure***.
- **Treatment** of this case needs putting the premature babies in **incubator** and administration of surfactant **locally** in the lung.

4. **Cephalin (phosphatidyl ethanolamine):**
   *a)* **Structure:** Like lecithin but it contains ethanolamine instead of choline.
   *b)* **Function:** It is one of activating factors of coagulation mechanism.

5. **Lysophospholipids (lysolecithin and lysocephalin):**
   *a)* **Structure:** Like lecithin and cephalin, but contains only one fatty acid in position 1 (α).
   *b)* **Functions:**
      1) Lysolecithin is important in the metabolism and inter conversion of phospholipids (see lipids metabolism, part II).
      2) Lycocephalin is strong surface-active substance. It is used in manufacturing most types of chocolates.

6. **Phosphatidylserine:**
   *a)* **Structure:** like lecithin but it contains serine instead of choline. (Notice that phospholipids containing threonine are also present).

7. **Lipositol (phosphatidylinositol):**
   *a)* **Structure:** Like lecithin but it contains inositol instead of choline.
   *b)* **Function:** It is present in cell membrane. It acts as precursor of second messenger (inositol triphosphate), mediating hormonal action inside cells (see hormones, part II).

**8. Plasmalogens:**

*a)* **Structure:** Like lecithin but it contains unsaturated alcohol attached to glycerol at position 1(α) by other linkage instead of unsaturated fatty acid.

**Function:** They constitute about 10% of the phospholipids present in brain and muscles.

**9. Sphingomyelins:**

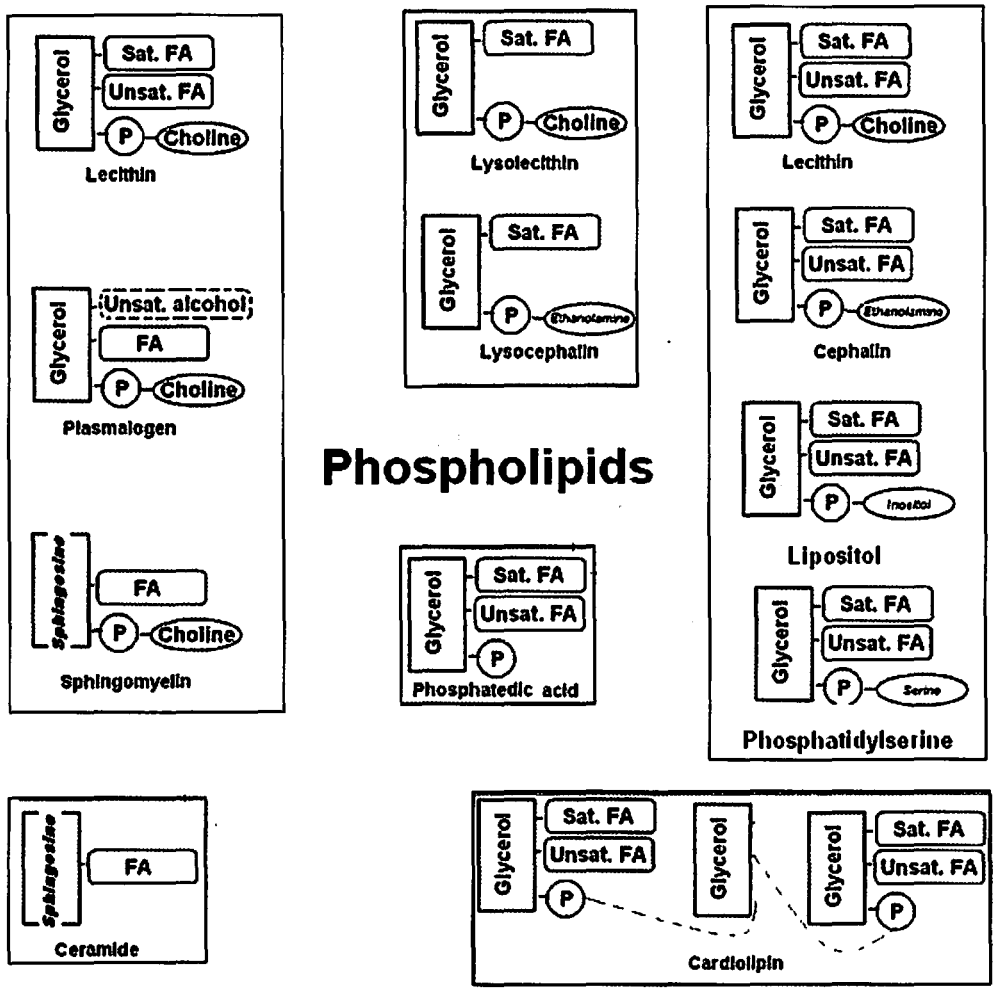
*a)* **Structure:**

1) Sphingosine.
2) Fatty acid (attached to amino group at position 2(β).
3) Phosphoric acid residue (attached to 3 (α) position).
4) Choline base (attached to phosphoric acid).

*b)* **Function:** It is present in high concentrations in brain and nerve tissue.

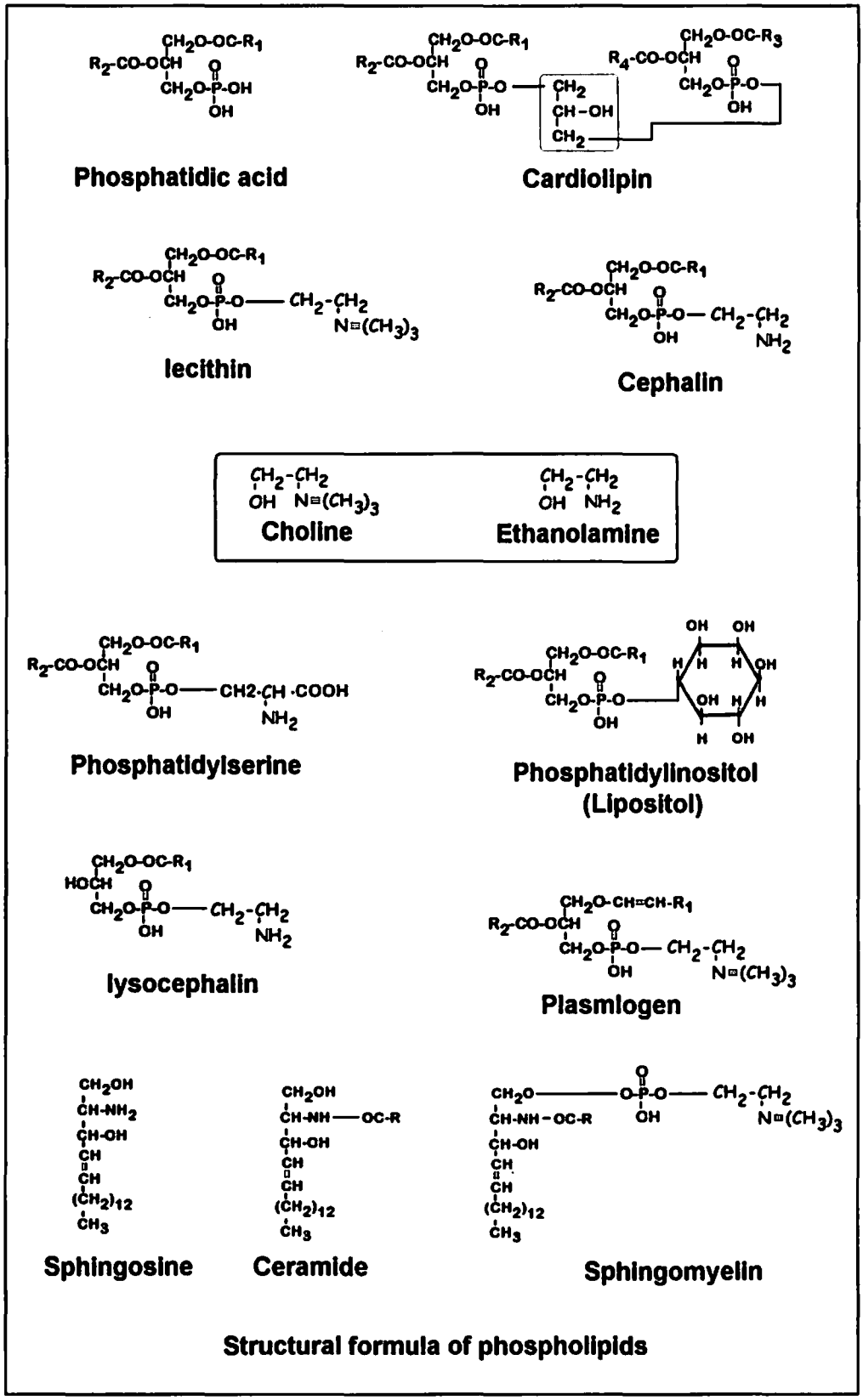
*c)* **Niemann Pick's disease:**

1) It is accumulation of large amounts of sphingomyelin in liver due to deficiency of sphingomyelinase enzyme.
2) It leads to mental retardation and death in early life.



**10.Ceramide:** It is not a phospholipid, but found in glycosphingolipids (see below).

*a)* **Structure:** Sphingosine + fatty acid (usually polyunsaturated).

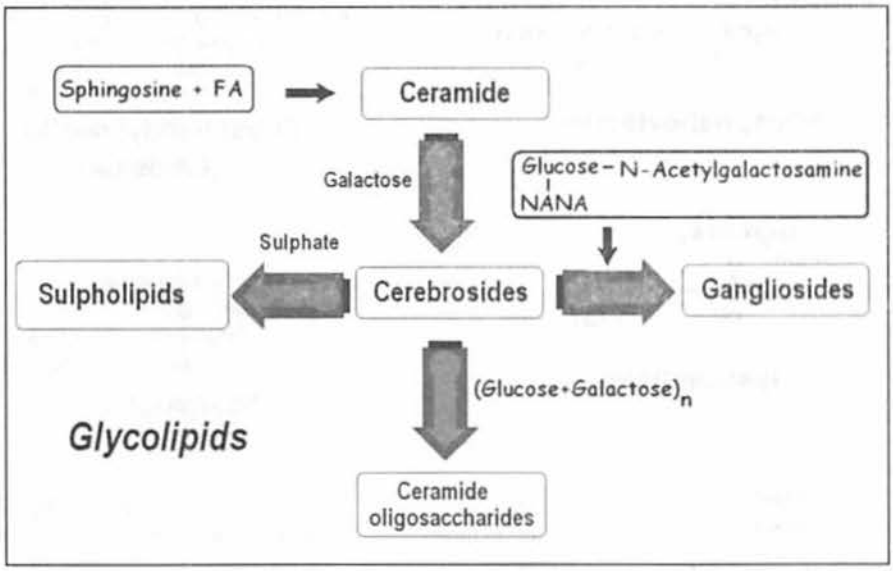



**Structural formula of phospholipids**

***Summary of functions of phospholipids:***

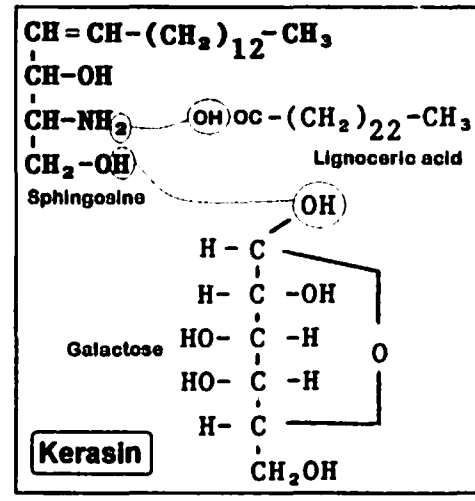
1. Phospholipids are present in **every body cell (cell membrane)**
2. phospholipids **act as lipotropic factor** i.e. prevent accumulation of fat in liver (fatty liver).
3. Phospholipids containing choline, (e.g. lecithin) are important in **nerve transmission** and also act as **methyl donor** in transmethylation reactions.
4. Dipalmitylecithin acts as a **lung surfactant.** It prevents adherence of alveolar wall.
5. Cephalin has a role in **coagulation** mechanism.
6. Phosphatidylinositol (lipositol) acts as a precursor of **second messenger,** mediating hormonal action inside cells.

**B. Glycolipids:** These are complex lipids containing **carbohydrate.** They also contain **sphingosine** *(therefore, glycolipids together with sphingomyelin may be classified as **sphingolipids**).* Glycolipids include cerebrosides, ganglioside, ceramide oligosaccharides and sulpholipids.



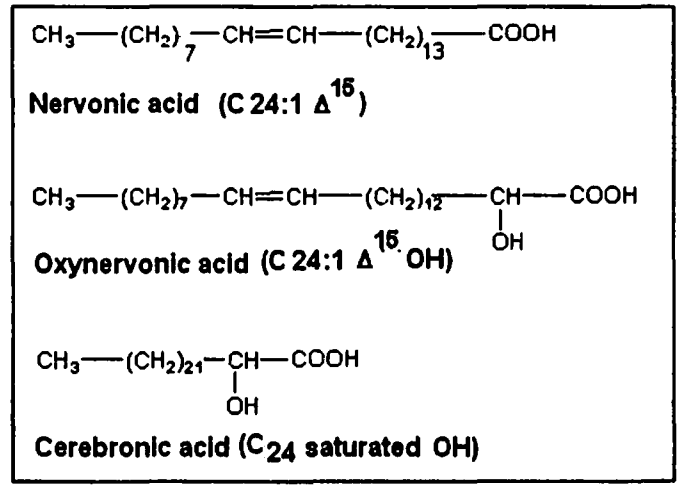

1. **Cerebrosides:** They are called simple glycolipids.
   *a)* Upon hydrolysis ,they give:
      1) Sphingosine.
      2) Fatty acid.
      3) Sugar (usually galactose or glucose).
   *b)* According to the **type of fatty acid**, they may be classified into:

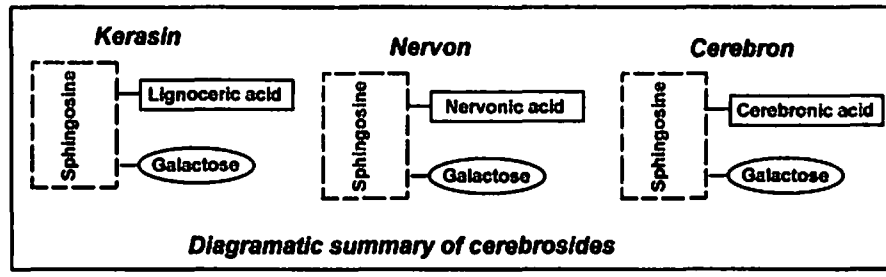
1) **Kerasin:** The fatty acid is lignoceric acid ($C_{24}$: saturated).
2) **Nervon:** The fatty acid is nervonic acid ($C_{24}$-unsaturated,$\omega^9$).
3) **Oxynervon:** The fatty acid is oxynervonic acid (hydroxy nervonic acid).
4) **Cerebron:** The fatty acid is cerebronic acid ($C_{24}$-hydroxy saturated).




*c)* **Functions of cerebrosides:**

1) Cerebrosides are present in many tissues especially in the brain and myelin of nerve fibres.
2) They act as insulators of nerve impulse.



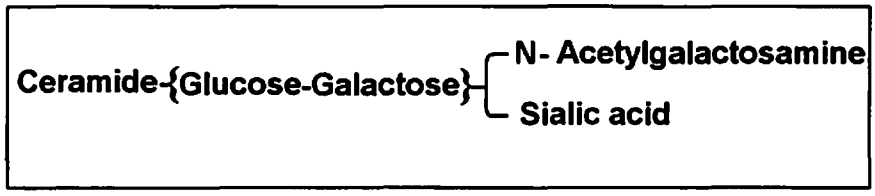



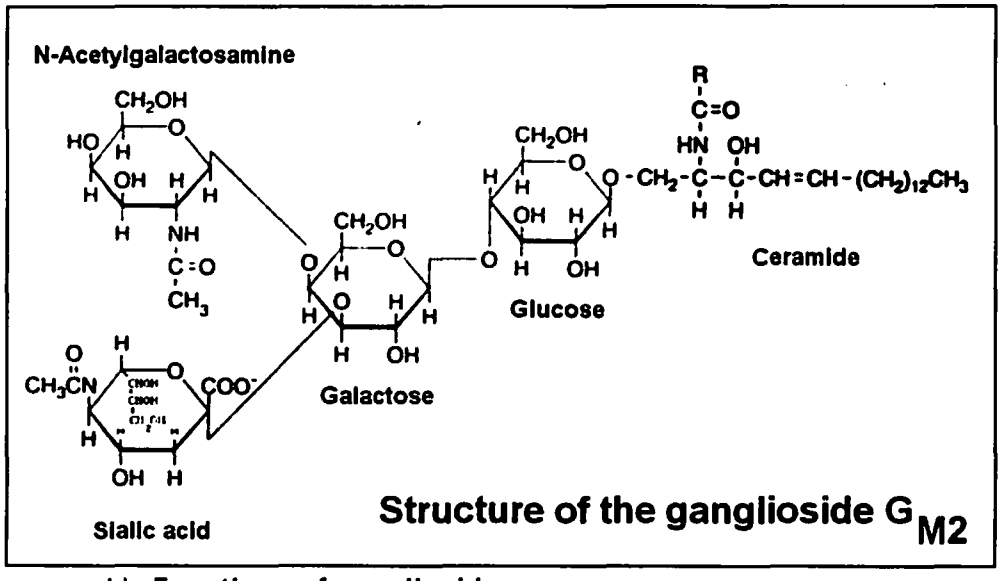

*d)* **Gaucher,s disease:**

1) Accumulation of cerebrosides (sphingolipids) in phagocytes due to deficiency of β **glucocerebrosidase** enzyme.
2) **Manifestations:** mental retardation, hepatomegally and bone disorders.

2. **Sulpholipids** (sulphatides): are cerebrosides containing sulphate group (attached to sugar).

3. **Gangliosides:** They are called complex glycolipids, because they contain in addition to hexose, one or more sialic acid molecules.
   *a)* **Upon hydrolysis they give:**
      1) Ceramide (sphingosine and fatty acid).
      2) Hexoses (glucose and galactose).
      3) Hexosamines:
         - Sialic acid (N-acetylneuraminic acid).
         - N-acetylgalactosamine).




   *b)* **Functions of gangliosides:**
      1) They act as receptors at cell membrane.
      2) They are present in high concentration in brain.
   *c)* **Degradation:** By **hexosaminidase** enzyme.
   *d)* **Tay sachs disease:**
      1) Accumulation of gangliosides in brain and intestine due to deficiency of **hexosaminidase** enzyme.
      2) **Manifestations:** mental retardation, hepatomegally, blindness and death in early life.
4. **Ceramide oligosaccharides:** They contain sphingosine base, fatty acid ($C_{24}$) and many glucose and galactose units. They are present in heart and kidney.

C. **Lipoproteins:** These are complex lipids formed of lipids conjugated with protein.

1. **They are present in** cell membrane, mitochondria and plasma (plasma lipoproteins).
2. Plasma lipoproteins convert water insoluble lipids into water soluble complexes. This facilitates transport of lipids between blood and different tissues.
3. **The plasma lipids (360 – 820 mg/dl) are** triacylglycerols, phospholipids, cholesterol (free and esterified) and free fatty acids.

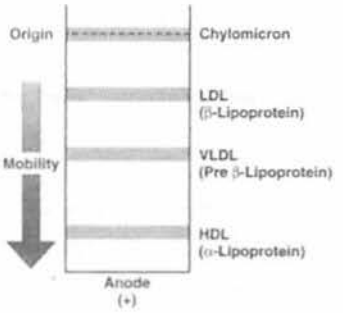
| | |
|---|---|
| 1-Cholesterol : | **140-220 mg/dl**<br>**70% Cholesteryl esters**<br>**30% Free cholesterol** |
| 2-Phospholipids : | 150-200 mg/dl |
| 3-Triacylglycerols : | 40-160 mg/dl |
| 4-Free fatty acids : | 8-16 mg/dl |

4. **<u>Methods used for separation of plasma lipids:</u>**

These methods include electrophoresis, ultracentrifugation, gas liquid chromatography and thin layer chromatography:

*a)* **By electrophoresis,** plasma lipoproteins can be separated into chylomicrons, β-lipoproteins, pre-β-lipoproteins and α-lipoproteins.

*b)* **By ultracentrifugation**, plasma lipoproteins can be separated into chylomicrons, VLDL, LDL and HDL.



Electrophoretic mobility of plasma lipoproteins.

5. The protein fractions are called apolipoproteins. They include apolipoproteins A, $B_{48}$, $B_{100}$, C, D and E. All are globulins.

| FRACTION | SOURCE | MAIN LIPID | APOLIPOPROTEINS Amount | APOLIPOPROTEINS Types |
|---|---|---|---|---|
| **Chylomicrons** | Intestine | TG | 2% | A, $B_{48}$, C &E. |
| **VLDL** | Liver | TG | 10% | $B_{100}$, C & E. |
| **LDL** | Blood from chylomicrons and VLDL | Cholesterol, cholesteryl esters and phospholipids | 22% | $B_{100}$ |
| **HDL** | Liver | Cholesterol, cholesteryl esters and phospholipids | 50% | A, C, D &E. |
| **FFA-Albumin** | Adipose tissue | FFA | 99% | Albumin |

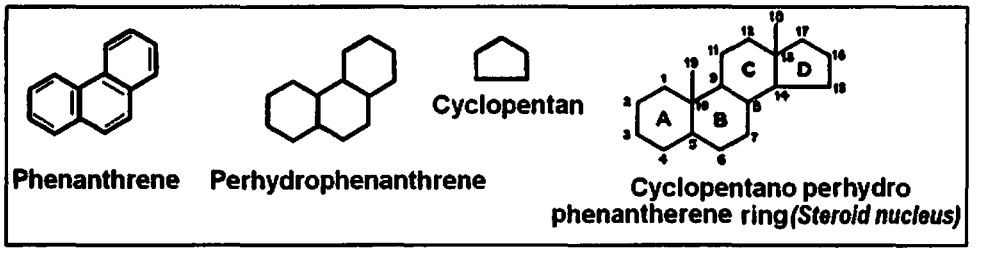
# Derived lipids

**I.** Substances which are insoluble in water but soluble in nonpolar solvents. They include:

1. Steroids and sterols.
2. Carotenoids
3. Cholanthrenes
4. Ketone bodies.
5. Fatty aldehydes.

## II. *Steroids and sterols*:

**A.** These are a group of compounds that contain ring called cyclopentano-perhydrophenanthrene ring.




**B.** The ring is characterized by the presence of the following atoms or groups:

1. **At $C_3$**: oxygen in the form of hydroxy (-OH) or ketone (=O) group.
2. **At $C_{17}$**: Side chain.
3. **At $C_{10}$ and $C_{13}$**: Methyl groups.
4. Steroids and sterols differ from each other in the nature of side chain (at $C_{17}$).

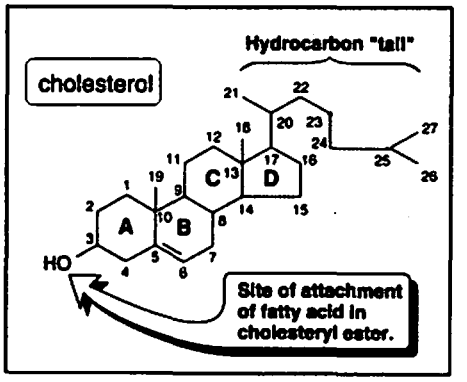
## III. Types of steroids and sterols are:

*Types of steroids and sterols are:*

1. Cholesterol (animal origin).
2. Ergosterol (plant origin).
3. Vitamin D group ($D_2$ and $D_3$).
4. Bile salts.
5. Steroid hormones:
   - *a)* Male sex hormones.
   - *b)* Female sex hormones.
   - *c)* Adrenocortical hormones.
6. Digitalis glycosides.
7. Some carcinogenic substances

### A. Cholesterol:

1. **Structure:** It contains:
   - *a)* Cyclopentano-perhydrophenanthrene ring.
   - *b)* -OH group at $C_3$ (so it is an alcohol).
   - *c)* 2 methyl groups at $C_{10}$ & $C_{13}$ (-$CH_3$ = I).
   - *d)* Long side chain at $C_{17}$.



2. **Body cholesterol:**
   *a)* It is present in every body cell (cell membrane) especially in:
      1) Adrenal cortex.
      2) Gonads.
      3) Liver and kidney.
      4) Brain and nerve tissue.
   *b)* **Blood cholesterol:**
      1) It occurs in the blood in 2 forms: free form and esterified form (combined to fatty acids to form ester).
      2) The level of blood cholesterol is normally less than 220 mg/dl. Any increase above this level is called: **hypercholesterolemia.**

3. **Properties:**
   *a)* It is an alcohol, insoluble in water, soluble in fat solvents.
   *b)* It forms characteristic crystals with broken corner.
   *c)* It gives positive Lieberman's test, which runs as follows:

| **Cholesterol + Acetic acid + conc. sulphuric acid → Bluish green color.** |
|---|

   *d)* It is present only in animals and not in plants.

4. **Functions of cholesterol:** it is important for:
   *a)* It enters in the **structure of every body cell** particularly:
      1) Cell membranes.
      2) In nervous tissue.
   *b)* **Synthesis of steroid hormones.**
   *c)* **Synthesis of bile salts.**
   *d)* **Synthesis of vitamin $D_3$.**

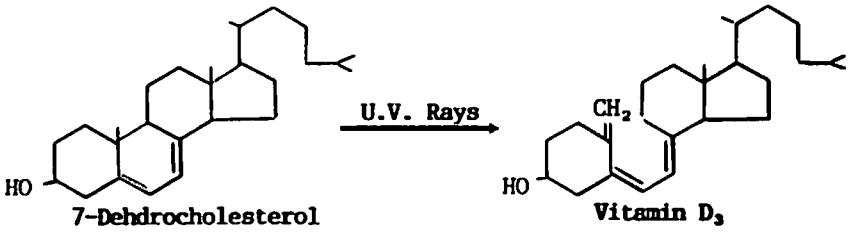
5. **Coprastanol (coprosterol):** Some cholesterol is synthesized in the intestine and reduced by intestinal bacteria into **coprastanol** before excretion (by reduction of double bond of cholesterol between $C_5$ and $C_6$).

B. **<u>Ergosterol</u>:**
1. **Structure:** Similar to cholesterol but differs in:
   *a)* Extra double bond between $C_7$, $C_8$.
   *b)* The side chain is unsaturated and has extra methyl group.
2. **Properties:** It is a plant sterol, poorly absorbed from small intestine.
3. **Functions:** It gives vitamin $D_2$ by ultraviolet rays.

## C. Vitamin D group: (see chapter of vitamins):

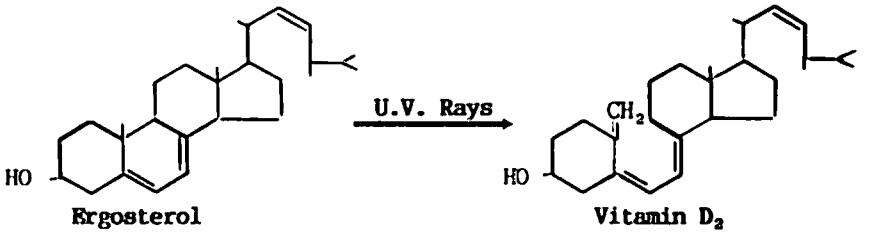
### 1. Structure:

*a)* Vitamin $D_3$ is derived from 7-dehydrocholesterol by the rupture of second ring by ultraviolet rays.




7-Dehdrocholesterol — Vitamin $D_3$

*b)* Vitamin $D_2$ is derived from ergosterol by the rupture of second ring by ultraviolet rays.

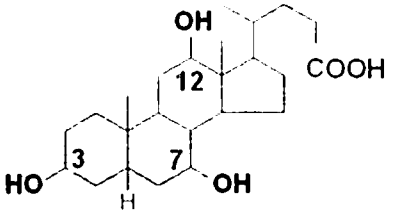



Ergosterol — Vitamin $D_2$

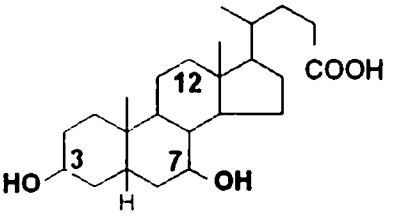
### 2. Functions: see vitamins.

## D. Bile acids and salts: Bile acids are hydroxyl derivatives of C24 steroid termed cholanic acid.

### 1. Types of bile acids:

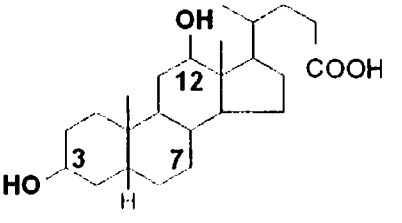



Cholic acid

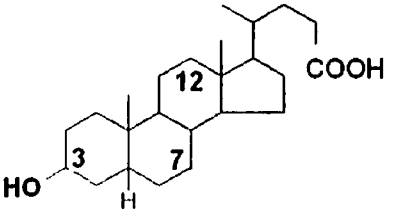



Chenodeoxy cholic acid

**Primary bile acids**




Deoxycholic acid



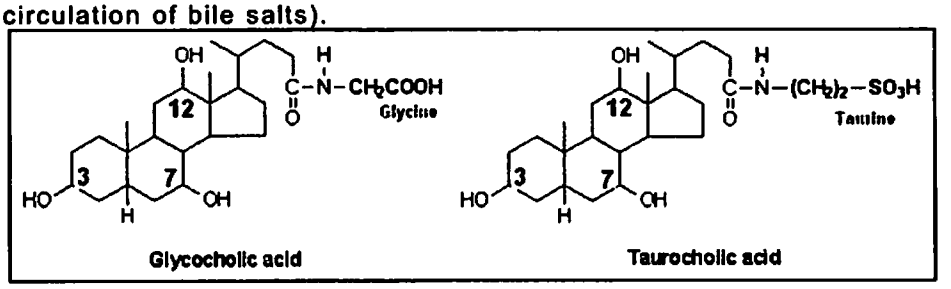

Lithocholic acid

**Secondary bile acids**

*a)* **Primary bile acids:** these are formed in the liver from cholesterol and include cholic acid (3,7,12 trihydroxy cholanic acid) and chenodeoxy cholic acid (3,7 dihydroxy cholanic acid).

*b)* **Secondary bile acids (no –OH at C7):** These are formed by the action of intestinal bacteria that contain 7 α dehydroxylase which removes the hydroxyl group at C7, with production of 2 types of secondary bile acids : deoxycholic acid (3,12 dihydroxy cholanic acid) and lithocholic acid (3 monohydroxy cholanic acid).

2. **Bile salts** are bile acids (=cholic acid) conjugated with glycine (80%) and taurine (20%), they are excreted by liver in bile as sodium salts e.g. sodium glycocholate and sodium taurocholate. Bile salts pass to the intestine where they are reabsorbed and return back to the liver to be excreted again in bile (enterohepatic circulation of bile salts).




3. **Function:** Bile salts are **amphipathic** and important for digestion and absorption of lipids:

*a)* **Digestion of lipids:** by emulsification of fat in the intestine and activation of lipase enzyme.

*b)* **Absorption of lipids:** by forming micelles.

*c)* **Excretion of cholesterol:** Half of cholesterol is excreted after its conversion into bile salts.

*d)* **Choleretic effect**: i.e. bile salts stimulate liver cells to secret more bile.

*e)* Prevent formation of **cholesterol stones** by keeping cholesterol in soluble state.

**Steroid Hormones:**
* **Female sex hormones**
* **Male sex hormones**
* **Adrenocortical hormones**

## E. Hormones of steroid nature:

### 1. Female sex hormones:

*a)* **Estrogens:** There are 3 types: estrone (E1), estradiol (E2) and estriol (E3). E2 is the most active member.

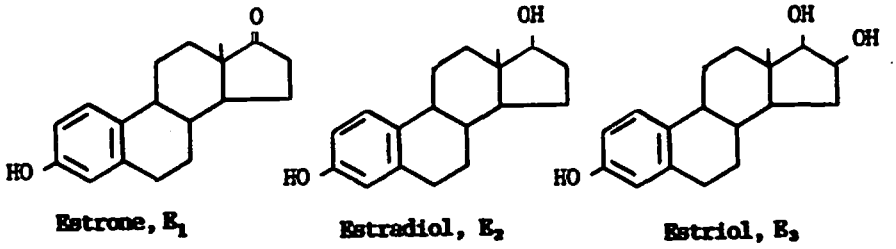
1) **Structure:**

i- Hydoxyl group at $C_3$.

ii- Ring A is unsaturated.

iii- Methyl group at $C_{13}$

iv- Ketone group at $C_{17}$ (E1), hydroxyl group at $C_{17}$ (E2) and 2 hydroxyl groups at $C_{16}$ & $C_{17}$.




**Estrone, $E_1$** **Estradiol, $E_2$** **Estriol, $E_3$**

2) **Synthesis**: *From cholesterol.*

**Cholesterol → Androstenedion → Testosterone**
**Aromatase + $-CH_3$ → Estradiol ($E_2$) → $E_1$ + $E_3$**

3) **Site of production:**

i- **Mainly:** ovary and placenta in female.

ii- **Minor amounts:**

- Adrenal cortex in both male and female.
- Testes in males.

4) **Functions:**

i- They stimulate the development of female **secondary sex characters** and organs e.g. voice, distribution of hair, distribution of fat, ...

ii- They stimulate the development of **female sex organs** e.g. uterus.

iii- $E_2$ has **anabolic effects** on bone and cartilages.

5) **Contraception:** synthetic estrogens can be used as contraceptives.

6) **Fate:** End product $E_3$ are produced in the liver and conjugated with sulphuric acid and glucuronic acid and then excreted in the urine.

*b)* **Progesterone:**

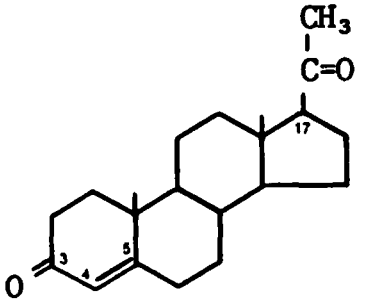
1) **Structure:**

i- Ketone group at $C_3$.

ii- Double bond between $C_4$ and $C_5$.

iii- Methyl group at $C_{10}$ & $C_{13}$.

iv- Methyl ketone at $C_{17}$.




**Progesterone**

2) **Site of production:**

i- Ovary and placenta in female.

ii- Adrenal cortex in both male and female.

3) **Functions of progesterone:**

i- It prepares the uterus for implantation of the ovum.

ii- It stabilizes pregnancy (it prevents abortion).

iii- It stimulates breast acini during puberty and pregnancy.

iv- It inhibits milk production in late pregnancy. Progesterone decreases sharply after delivery causing lactation.

v- Antagonizes the action of estrogens at various tissues.

4) **Fate:** In the liver, the end product is pregnadiol which is conjugated with sulphuric acid and glucuronic acid and then excreted in urine.

**2. Male sex hormones:**

*a)* **Androgens (testosterone and dihydrotestosterone, DHT):**

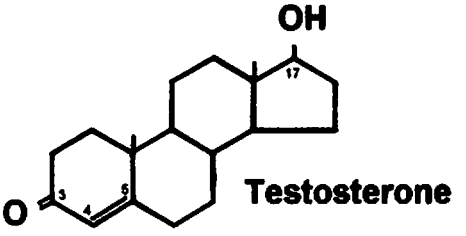
1) **Structure:**

i- Ketone group at $C_3$.

ii- Double bond between $C_4$ and $C_5$.

iii- 2 methyl group at $C_{10}$ & $C_{13}$.

iv- -OH at $C_{17}$.



Testosterone

v- **Dihydrotestosterone (DHT)** has the same structure of testosterone without double bond between C4 and C5. It is the active form of testosterone at tissues.

**Testosterone + NADPH+H+ $\xrightarrow{\text{Reductase}}$ DHT**

2) **Site of production:**

i- Interstitial cells of leyding of the testes in male.

ii- Adrenal cortex in both male and female.

3) **Functions:**

i- They stimulate the development of male sex character and organs as voice, distribution of hair, distribution of fat etc.

ii- They stimulate sperms formation (spermatogenesis).

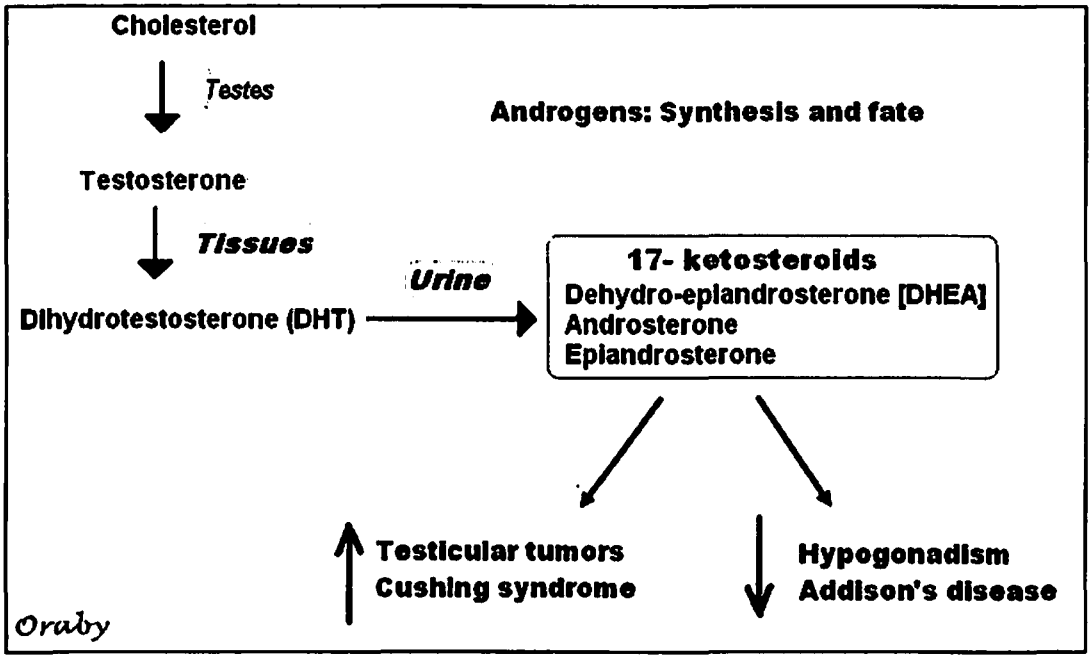
iii- They have anabolic effect on proteins.

4) **Fate:** The end products are 17-keto steroids (comounds having = O instead of –OH at $C_{17}$) which is excreted in the urine.

i- 17 Ketosteroids include dehydro-epiandrosterone acetate (DHEA), androsterone, and epiandrosterone.

**ii- Variations in urinary 17 ketosteroids:**

- **Increased in testicular tumors and hyperfunctions of adrenal cortex e.g. Cushing syndrome.**
- **Decreased in hypogonadism and hypofunction of adrenal cortex e.g. Addison disease.**




**3. Adrenal cortical hormones (= Glucocorticoids and mineralocorticoids):**

*a)* **Structure:**

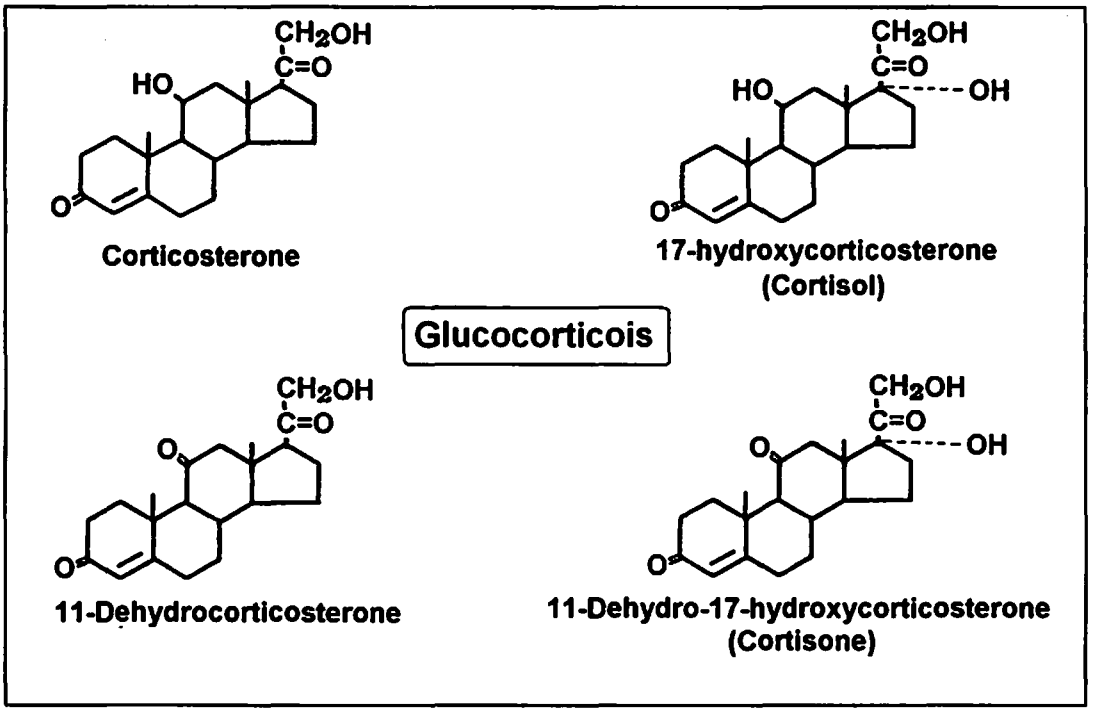
1) All have a ketone group at $C_3$.
2) All have double bond between $C_4$ ,$C_5$.
3) All have a methyl groups at $C_{10}$.
4) All have a methyl groups at $C_{13}$ (except aldosterone which has –CHO group).
5) All have a ketol group at C17.
6) All have an -OH group or oxygen at $C_{11}$,(except DOC).

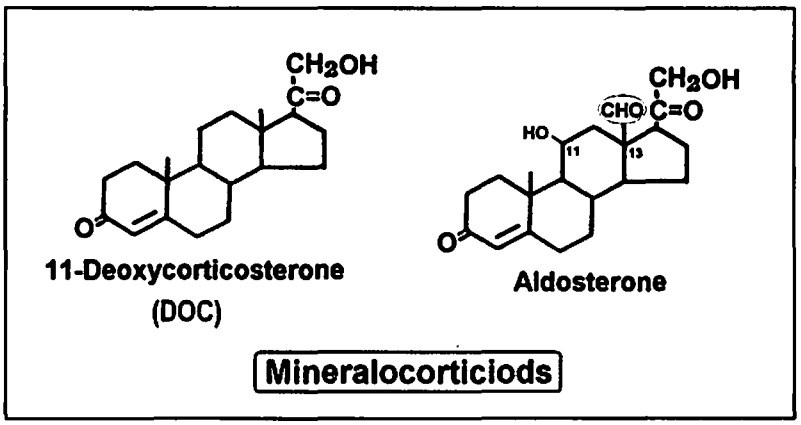
*b)* **Site of production:** are derived from cholesterol in adrenal cortex of suprarenal glands.

*c)* **Types:**

1) **Glucocorticoids:** include corticosterone, cortisol, cortisone and 11-dehydrocorticosterone.
2) **Mineralocorticoids:** include aldosterone and deoxycorticosterone (DOC).

**Note:** The synthetic derivative of DOC is called deoxycorticosterone acetate (DOCA), which is used in treatment of Addison disease (=cortical hypofunction).



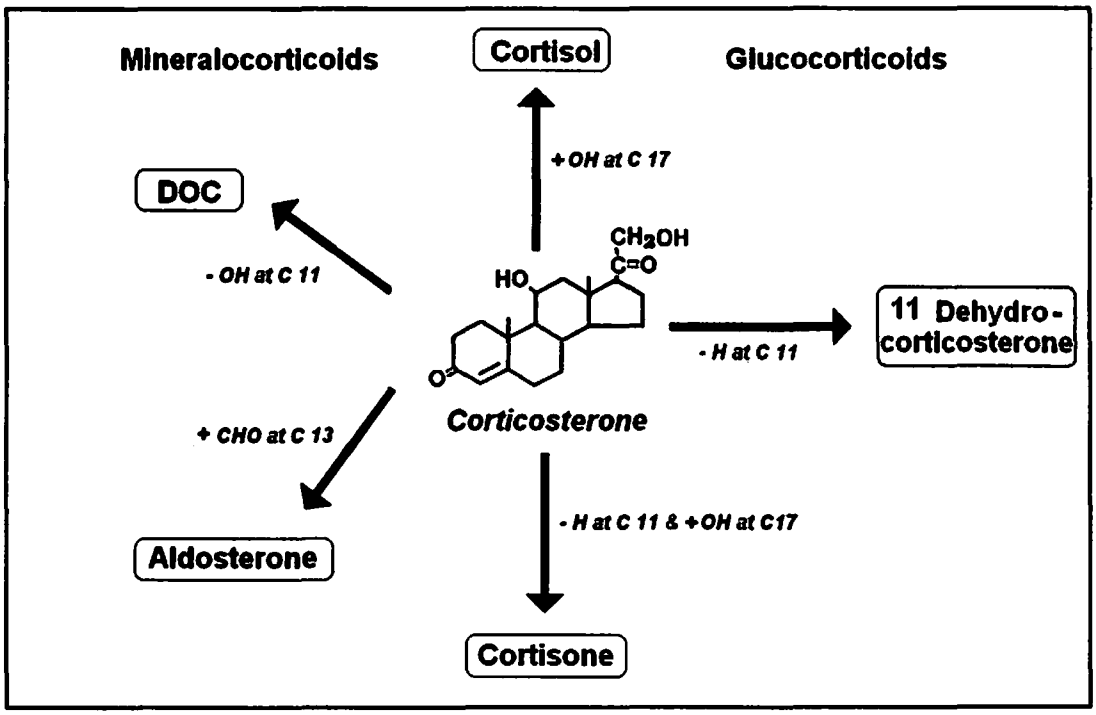




*d)* **Functions:**

1) **Glucocorticoids:** Control the metabolism of carbohydrate, protein and fat.
   - i- Have catabolic effect (breakdown) on proteins and lipids.
   - ii- Have anabolic effect on carbohydrate: have anti-insulin effect, inhibit glucose oxidation and stimulate gluconeogenesis.
2) **Mineralocorticoids:** Control the metabolism of minerals. They act mainly on kidneys where it promotes secretion of $K^+$ and $H^+$ and reabsorption of $Na^+$.

*e)* **Variations:**

1) **Hyperfunctions:** ↑ Glucocorticoids →Cushing disease.
2) **Hypofunctions:** ↓ Glucocorticoids and mineralocorticods →Addison's disease.




**IV.*Other derived lipids:*** Carotenoids, Cholantherene and Polyprenoids

**A. <u>Carotenoids (terpenes)</u>:**

**1. Definition:**

*a)* Carotenoids are among the most common and most important natural pigments.

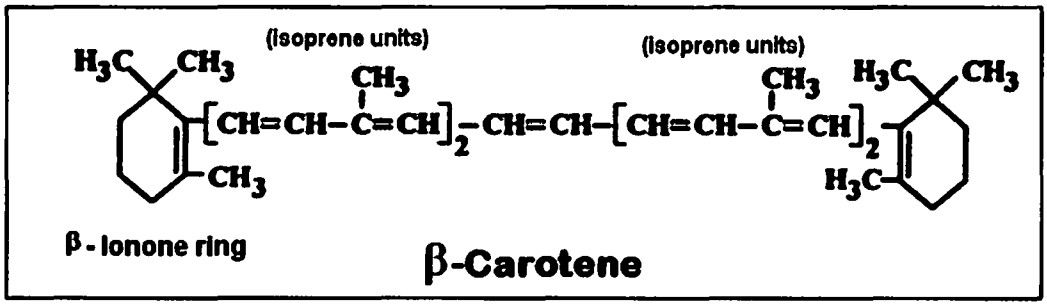
*b)* They have yellow to red color.

**2. Types and structure:**

*a)* Many types are present e.g. α, β, and γ carotene.

*b)* All are hydrocarbons formed only of carbons and hydrogen.

*c)* Generally each carotene is formed of two ionone rings. Each ionone ring is connected to two isoprene units, both are interconnected by methane group (–CH=CH-).




**3. Sources:**

*a)* **Plant sources:** They are responsible for many colors of fruits and vegetables e.g. carrots, orange, apricot, apple and tomato.

*b)* **Animal sources:** fats, butter, milk and egg yolk.

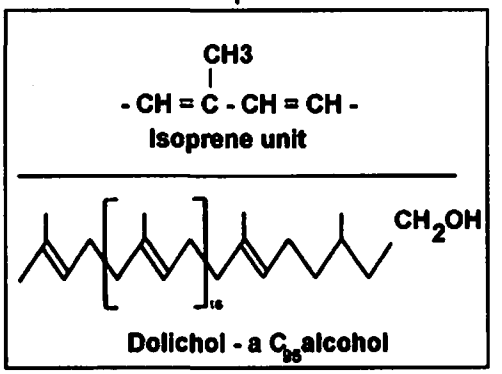
4. **Functions:**
   *a)* They have **antioxidant** and antimalignant properties.
   *b)* **Provitamin A:** They are converted into vitamin A in intestine (see chapter of vitamins).

**B. Cholantherene:**

1. These are derived lipids similar in structure to steroids with extra-methyl group. They are highly carcinogenic.

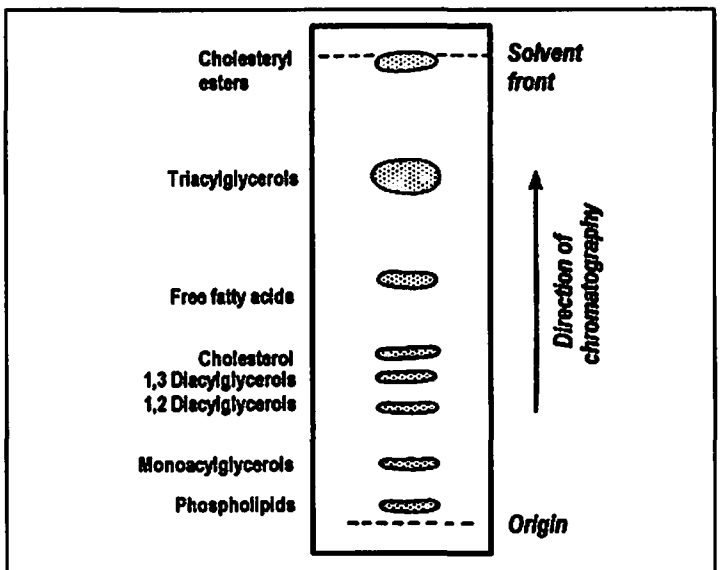
**C. Polyprenoids:** These are compounds related to steroids because they are synthesized like cholesterol from 5-carbon isoprene unit.

1. They include **upiquinone,** a member of the respiratory chain in mitochondria, and the long alcohol **dolichol** which takes part in glycoprotein synthesis.
2. Isoprenoid compounds derived from plants include rubber, camphor, the fat soluble vitamins (A, D, E and K) and β-carotene (provitamin A).




**V. *Methods of separation and identification of lipids in biologic material*:** Many methods may be used, which include:

**A.** Thin layer chromatography.
**B.** Gas liquid chromatography.
**C.** Extraction of lipid by a mixture of chloroform and methanol (2:1). This method is an old one and not used now.




*Seperation of major lipid classes by thin layer chromatography.*

*A suitable solvent system for the above would be hexane-diethyl ether-formic acid (80:20:2 v/v/v).*

## VI. *Amphipathic lipids*:

A. Amphipathic molecules are those formed of two parts:
   1. **Water insoluble part:** nonpolar or hydrophobic part.
   2. **Water soluble part:** polar or hydrophilic part.

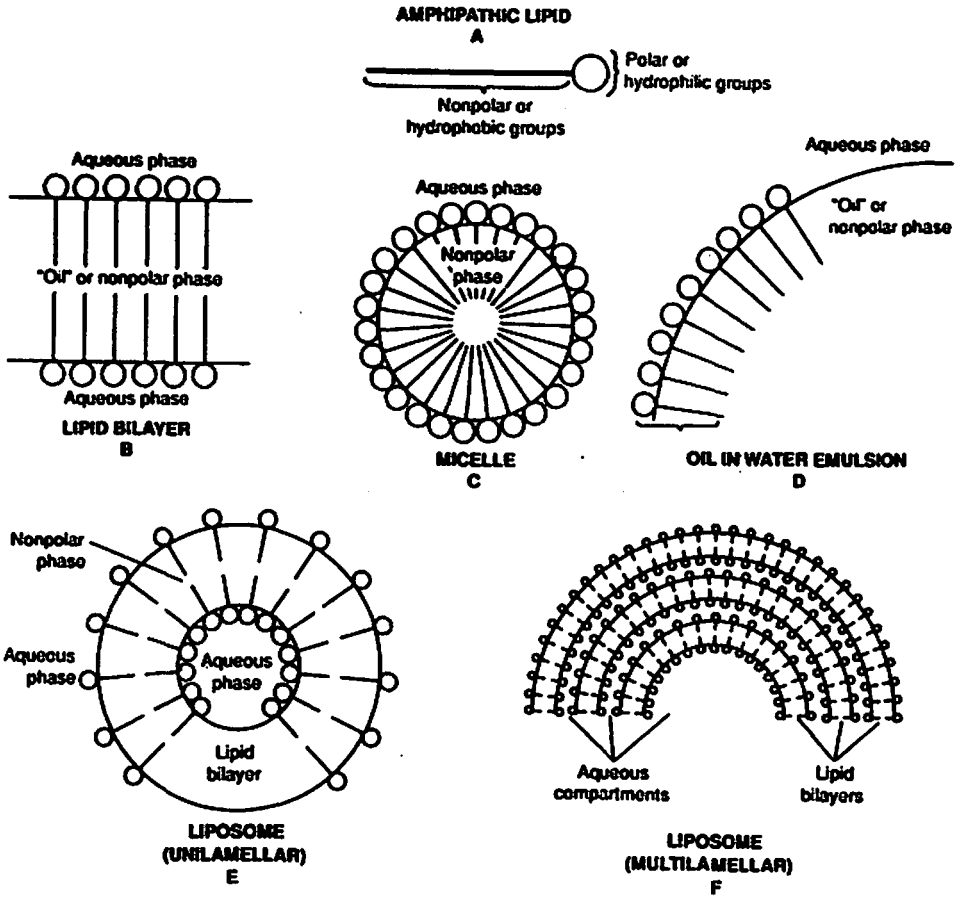
B. Lipids are insoluble in water except polar lipids like phospholipids and glycolipids.

C. ***Lipid bilayer:*** Phospholipids and glycolipids possess both **polar, hydrophilic groups** (glycerol, phosphate, nitrogen bases and inositol), and **nonpolar hydrophobic groups** (hydrocarbon chains of fatty acids and sphingosine). **A bilayer** of these lipids has been suggested as a basic structure in biologic membranes, the plasma, nuclear, mitochondrial and lysosomal membranes. In such membranes, the lipid molecules arrange themselves so that the nonpolar groups of the 2 layers are towards each other, while the polar groups are towards the surrounding aqueous phase.

D. **Micelles:** These are spheres of polar lipids, less than 0.5 μm in diameter, in which the nonpolar groups are at the centre, while the polar groups are at the periphery of the sphere, towards the aqueous phase. This process appears to be important in the absorption of fats from the intestine.

E. **Loposomes:** These are spheres of lipid bilayers enclosing a very small quantity of an aqueous phase. They are probably involved in the processes of pinocytosis (uptake of particles by the cell) and of exocytosis or emiocytosis (secretion of particles by the cell).

F. **Emulsions:** Relatively stable emulsions of nonpolar lipids in water can be obtained if we add small amounts of a polar lipids (e.g. phospholipids) before shaking. The molecules of the polar lipid surround the emulsion particles of the nonpolar lipid so that the nonpolar groups are towards inside, while the polar groups are towards the surrounding aqueous phase. Emulsification of fats is important in their digestion by the enzyme lipase in the intestine.

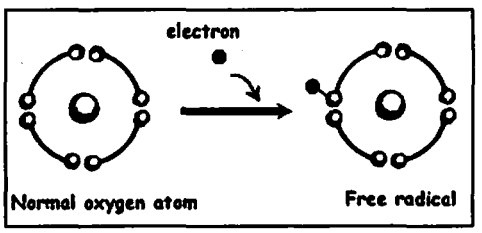



Formation of lipid membranes, micelles, emulsions, and liposomes from amphipathic lipids e.g. phospholipids.

# *Lipid peroxidation, free radicals and antioxidants*

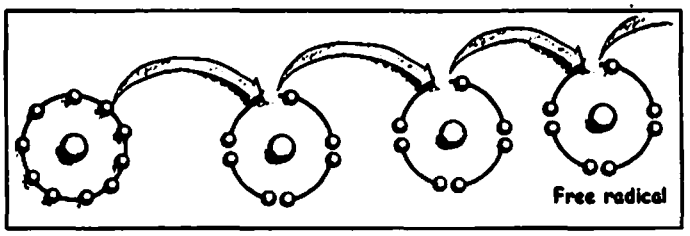
## *I.* ***Definition:***

**A.** Free radical is an atom or fragment of molecule having one or more unpaired electron; therefore, it will be very reactive and unstable. It is not positively or negatively charged.




**B.** Free radical will steal electron from another molecule creating a new one. When the free radical takes an electron from a molecule in a cell

wall, a new free radical is created and a chain reaction begins. This will affect the cell membrane leading to disintegration of the cell and results in **cell damage**.




C. Free radicals can be considered to be partially reduced metabolites of oxygen such as: superoxide anion $O^{\cdot\bullet}_2$, hydroxyl radical $OH^{\cdot\bullet}$ and $H_2O_2$. Peroxidation of unsaturated fatty acids creates also free radicals.

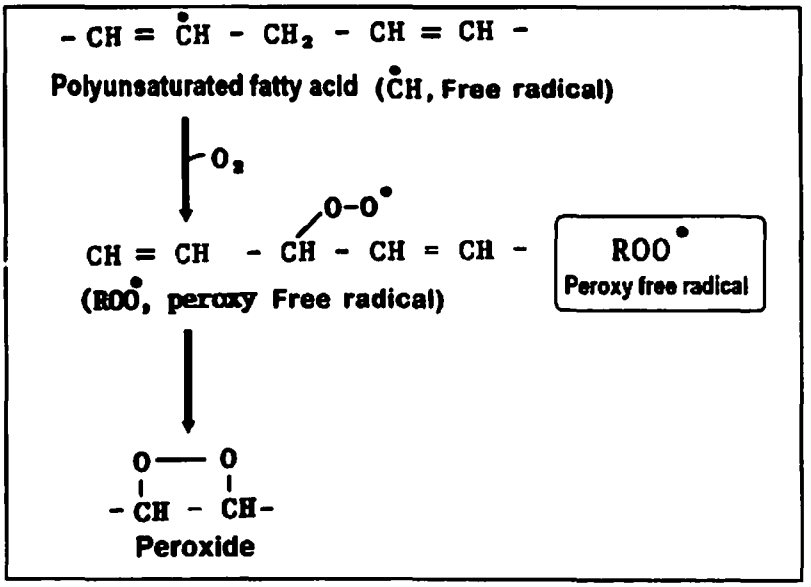
## *II. Sources of free radicals:*

A. **<u>Sources of superoxide free radicals $O^{\cdot\bullet}_2$</u>:**

1. Ischemia of mitochondria.
2. Vascular endothelium.
3. Circulating white cells such as neutrophils.
4. Conversion of hypoxanthine and xanthine to uric acid by xanthine oxidase enzyme.

B. **<u>Peroxidation of polyunsaturated fatty acids</u>**: Exposure of lipids containing polyunsaturated fatty acids to oxygen leads to their peroxidation (autooxidation).

1. Free radicals are produced during peroxide formation (peroxidation).
2. **Lipid peroxidation is a chain reaction** i.e. they provide continuous supply of free radicals which in turn initiate further peroxidation and so on. Initiation begins by light or metal ions.



C. **Other sources of free radicals:**

1. **Oxidation of catecholamines.**
2. **Activated neutrophils:**
   Free radicals produced by neutrophils are very important defensive mechanism against bacteria.
3. **Reactions with xenobiotic drugs** (foreign drugs) through **cytochrome $P_{450}$ system** of liver microsome (see chapter of xenobiotics).
4. **Cell ischemia** as in myocardial infraction.
5. **Exposure to sun light, osazone,** tobacco smokes and other environmental pollutants.
6. **X-rays and γ-rays** cause free radicals to form tissues.

## *III. Toxic effects of free radicals:*

A. **Cell damage:** by free radicals produced during lipid peroxidation (of unsaturated fatty acids) present in cell membrane.

B. **Atherosclerosis:**

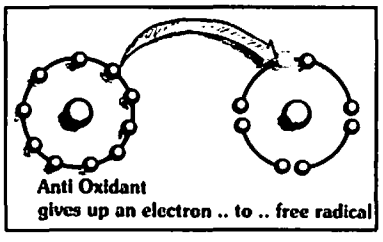
C. **Malignancy:** Free radicals can interact with DNA and other macromolecules, leading to molecular damage, mutation and carcinogenic effect.

D. **Aging process:** Free radicals may be a cause of aging process in the form of weakened immune system, some inflammatory diseases like rheumatoid arthritis, cataract, etc.....

E. **Oxidation of -SH groups in protein:** This leads to loss of biological activity of proteins and some enzymes.

F. **Myocardial infraction:** Ischemic myocardial cells i.e. cells suffering from oxygen lack, may produce free radicals such as superoxide ($O^{-\bullet}_2$) and hydroxyl ($OH^{\bullet}$) radicals. They damage myocardial cells by causing lipid peroxidation, breakage of DNA strands and oxidation of -SH groups in proteins. This may lead to death.

## *IV. Antioxidants and prevention of toxic effects of free radicals:*




A. **Definition:** Antioxidants are substances (atoms) that can give up an electron to free radicals. This prevents their toxic effects.

B. **Types:**

1. **Artificial antioxidants:**
   *a)* **Propyl gallate,** butylated hydroxyanisol (BHA) and butylated hydroxytoluene (BHT) are examples of artificial antioxidants.

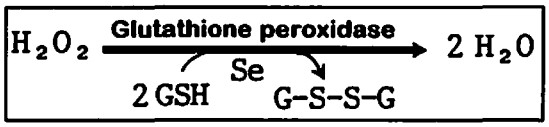
*b)* They are used as **food additives** i.e. added to foods to preserve them.

2. **Natural antioxidants:** They include naturally occurring substances such as Vitamin E (tocopherols), vitamin C, β-carotene and some enzymes (peroxidase and superoxide dismutase). They are further classified into preventive and chain breaking antioxidants.

*a)* **Preventive antioxidants:** They reduce the rate of chain initiation and include:

1) **Catalase enzyme:**


2) **Peroxidase enzyme** e.g. glutathione peroxidase. In which selenium trace metal (Se) is important for the action of this enzyme. It acts on $H_2O_2$ and reduced glutathione (GSH) converting them into $H_2O$ and oxidized glutathione (GS-SG).

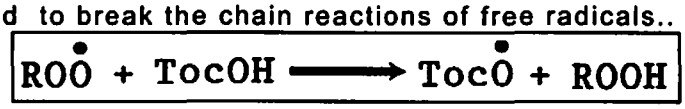



3) **Metal chelators:** They remove metals which may initiate fatty acids peroxidation. Metal chelators include EDTA (ethylenediamine-tetraacetate) and DTPA (diethylenetri-aminepentaacetate).

*b)* **Chain breaking antioxidants:** They interfere with chain propagation and include:

1) **Superoxide dismutase enzyme:** It acts on superoxide free radical ($O^{-\bullet}_2$)converting it to $H_2O_2$.


2) **Vitamin E (tocopherol, TocOH):** It has the ability to transfer a hydrogen atom of its phenolic group (-OH) to peroxyl free radical of polyunsaturated fatty acid. This will lead to break the chain reactions of free radicals..




3) **Vitamin C:**

i- It may react to regenerate tocopherol .

ii- It may react with 2 peroxyl free radicals converting them into non free radical product.


4) **Urate, phenols and other amines:** act as antioxidants.

# Chapter 3 — *Amino Acids, Peptides And Proteins*

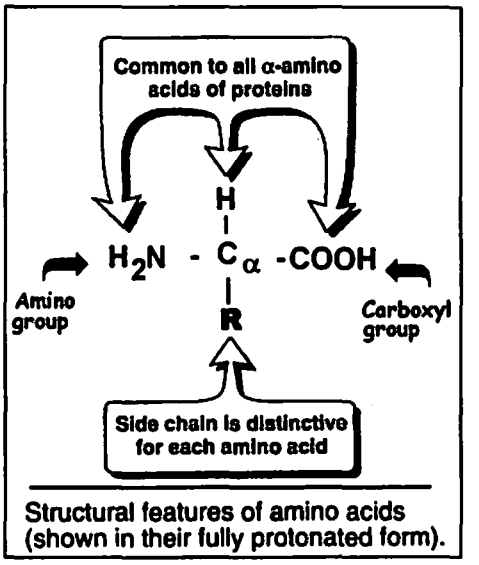
## *Amino Acids*

### I. *Structure:*

A. There are about 300 amino acids occurring in nature. Only 20 of them occur in proteins.

B. **Each amino acid has the following 4 groups or atoms**: attached to alpha (α)carbon:

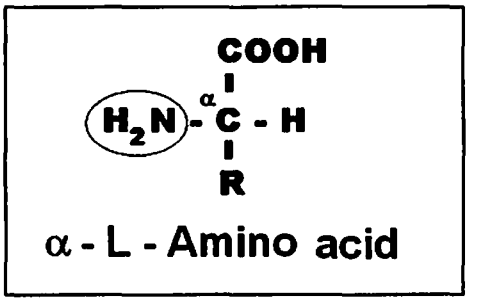
1. Amino group: ($NH_2$).
2. Carboxyl group: (COOH).
3. Hydrogen atom (H).
4. Side chain or radical group (R).



Structural features of amino acids (shown in their fully protonated form).

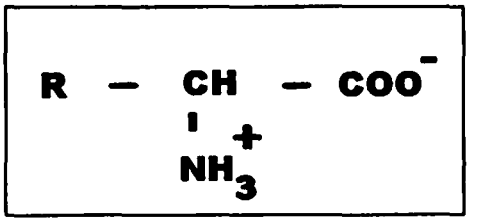
C. **Characters of amino acids**: all are

1. **α-Amino acids:** i.e. the amino group attached to the second carbon (next to the carboxyl group).
2. **L-Amino acid** i.e. α-amino group is on the left side configuration.



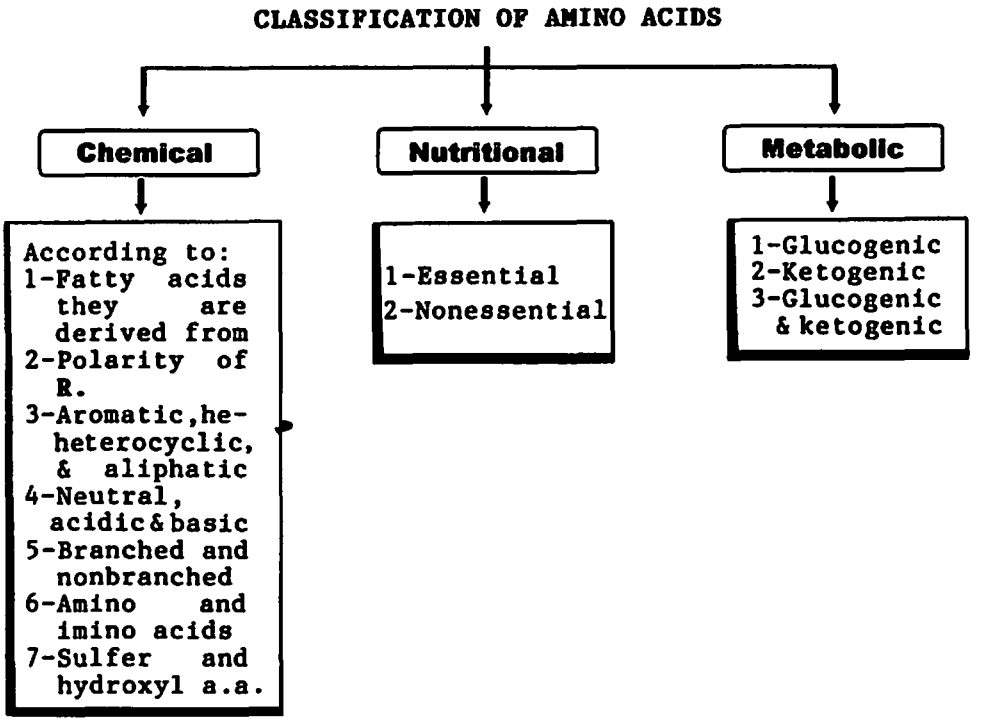

D. **One** of the 20 amino acids called **proline** is not an amino acid. It is an imino acid as it contains imino group (-NH).

E. **At physiological pH (approximately pH=7.4)** the carboxyl group is dissociated forming **a negatively charged carboxylate ion (-$COO^-$)** and the amino group is protonated, forming **positively charged ion (-$NH_3^+$).**



## II. *Classification of amino acids:*

Many methods are used to classify amino acids. The most common are chemical, nutritional and metabolic classifications.

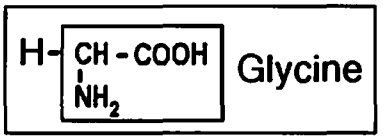



### Chemical classification *(7 methods)*:

A. **<u>According to the fatty acids the amino acids are derived from:</u>**

1. **Amino acids derived from acetic acid, (2 carbons) ($CH_3$-COOH):**

*a)* **Glycine:** (alpha amino acetic acid).

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2. **Amino acids derived from propionic, (3 Carbons) ($CH_3$-$CH_2$-COOH):**

*a)* **Alanine:** (alpha amino propionic acid)

*b)* **Phenylalanine:** (alpha amino,beta phenylpropionic acid)

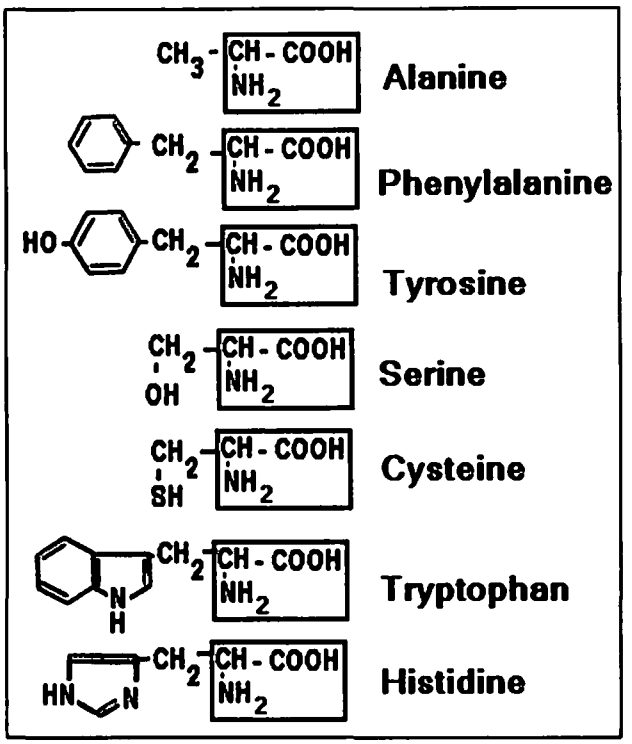
*c)* **Tyrosine:** (alpha amino, beta parahydroxy phenyl propionic acid)

*d)* **Serine:** (alpha mino betahydroxy propionic acid)

*e)* **Cysteine:** (alpha amino beta thiol,propionic acid)

*f)* **Tryptophan:** (alpha amino beta indole propionic acid)

*g)* **Histidine:** (alpha amino beta imidazol propionic acid)

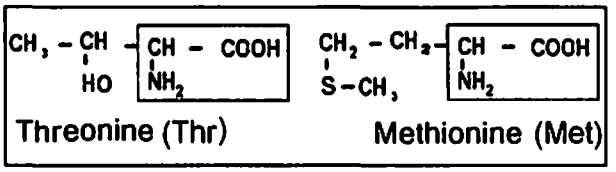



**3. Amino acids derived from butyric acid,** (4 Carbons)

**($CH_3$-$CH_2$-$CH_2$-COOH)**

**1) Threonine:**(alpha amino,beta hydroxy butyric acid)

**2) Methionine:**(alpha amino, gamma methyl thiol butyric acid)

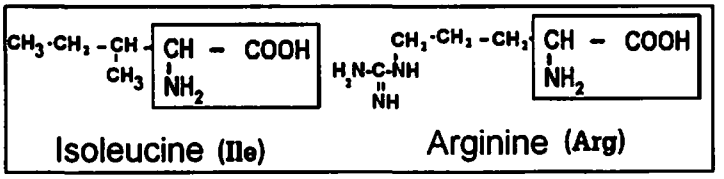



**4. Amino acids derived from valeric acid** (5 Carbons)

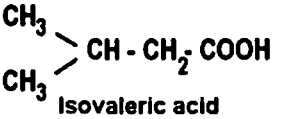
**($CH_3$-$CH_2$-$CH_2$- $CH_2$-COOH)**

**1) Isoleucine:**(alpha amino, beta methyl valeric acid)

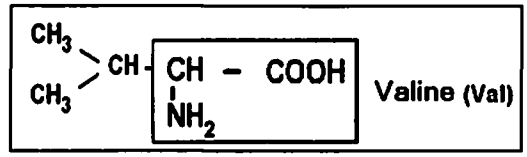
**2) Arginine:**(alpha amino, delta guanido valeric acid)




**5. Amino acids derived from isovaleric acid**
(5 Carbons):



**1) Valine:** alpha amino, isovaleric acid

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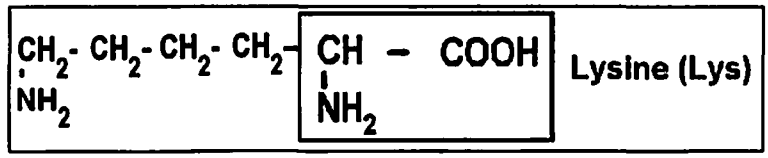
**6. Amino acids derived from caproic acid** (6 Carbons)

**($CH_3$-$CH_2$-$CH_2$- $CH_2$- $CH_2$- COOH)**

**1) Lysine:**(alpha amino, epsilon amino caproic acid)

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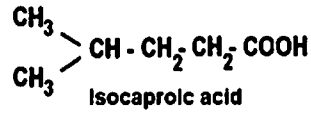
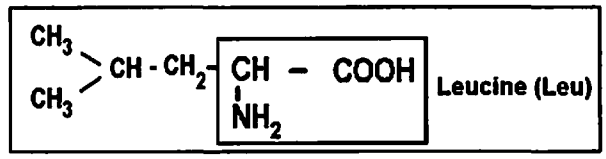
**7. Amino acids derived from isocaproic acid** (6 Carbons):




1) **Leucine:** (alpha amino isocaproic acid)

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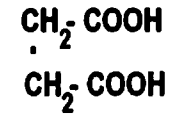
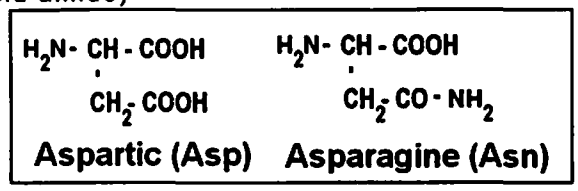
**8. Amino acids derived from succinic acid** (4 Carbons):




1) **Aspartate:** (alpha amino succinic acid)
2) **Asparagine:**(alpha amino succinic acid amide)

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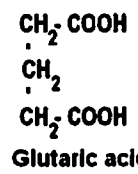
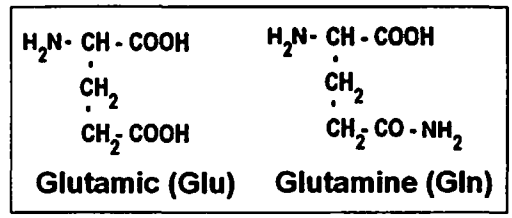
**9. Amino acids derived from glutaric acid:** (5 Carbons):

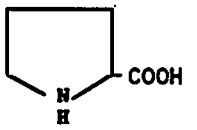


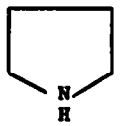

1) **Glutamate:**(alpha amino glutaric acid)
2) **Glutamine:** (alpha amino glutaric acid amide)



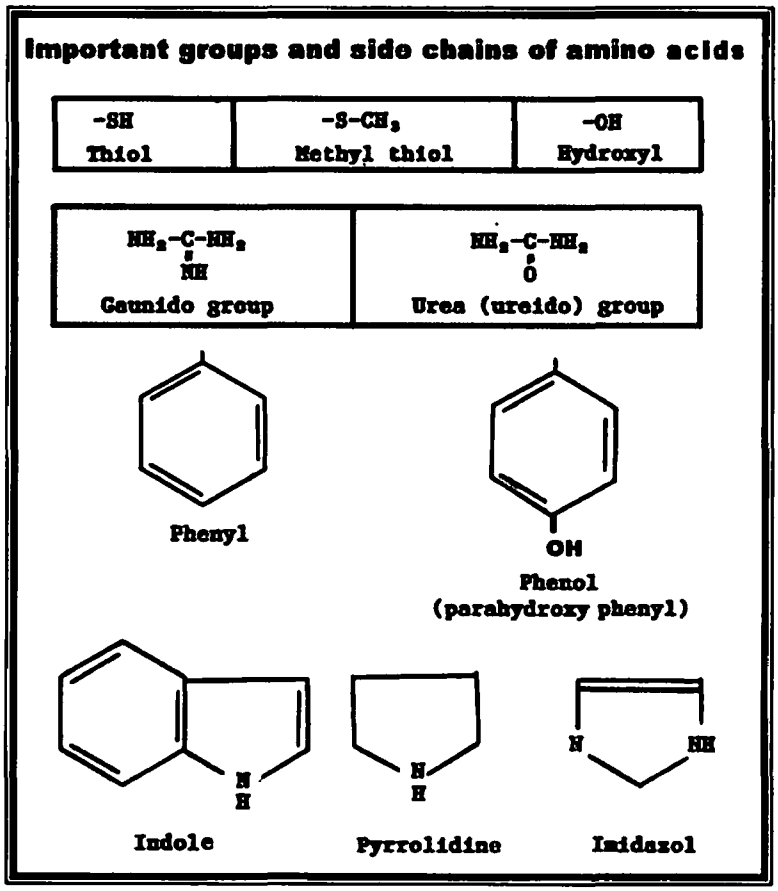
**10.Imino acids derived from pyrrolidine ring (4 Carbons):**

1) **Proline (P):**




Pyrrolidine

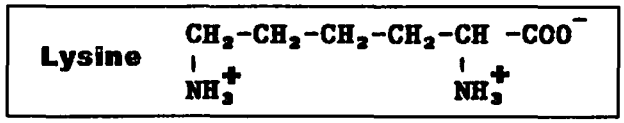



**B. <u>Classification according to the polarity of the radical (R)</u>:**

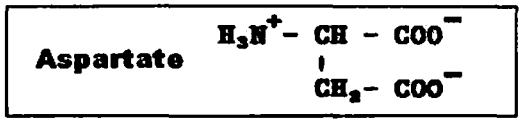
Amino acids (at pH : 6.0 - 7.0) are classified into 4 groups:

1. **Nonpolar (hydrophobic) amino acids:** least soluble amino acids and include: Glycine, alanine, phenylalanine, tryptophan, methionine, valine, leucine, isoleucine and proline.
2. **Polar hydrophilic neutral amino acids:** these are more soluble in water than the first group. The (R) group contains polar functional group which can bind with water by hydrogen bond. **They include:**
   *a)* **Sulfer containing amino acids:** cysteine.
   *b)* **Hydroxyl containing amino acids:** threonine, hydroxy-lysine, tyrosine and hydroxyproline.
   *c)* **Amide containing amino acids:** glutamine and asparagine.

3. **Polar hydrophilic basic amino acids:** Their (R) groups are positively charged: lysine, arginine and histidine.




4. **Polar hydrophilic acidic amino acids:** Their (R) groups are negatively charged: aspartate and glutamate.




C. **<u>Classification according to if amino acid is: aromatic, heterocyclic or aliphatic</u>.**

1. **Aromatic amino acids:** which contain phenyl or phenol ring:
   *a)* Phenylalanine (phenyl ring).
   *b)* Tyrosine (phenol ring).
2. **Heterocyclic amino acids:** which contain other type of rings:
   *a)* Tryptophan (indole ring).
   *b)* Histidine (imidazol ring).
   *c)* Proline (pyrrolidine ring).
   *d)* Hydroxyproline (hydroxypyrrolidine ring).
3. **Aliphatic amino acids:** include other amino acids which contain no ring.

D. **<u>Classification according to if the amino acid is acidic, basic or neutral amino acids:</u>**

1. **Acidic amino acids:** contain more than one **-COOH** group. e.g. aspartate and glutamate.
2. **Basic amino acids:** contain more than one **-$NH_2$** group. e.g. ornithine, lysine, arginine and histidine.
3. **Neutral amino acids:** these are amino acids, which contain one **-COOH** and one **-$NH_2$** groups. e.g. glycine, alanine, etc.

E. **<u>Classification according to if the amino acid is: branched or nonbranched:</u>**

1. **Branched amino acids:** valine, leucine and isoleucine.
2. **Nonbranched amino acids:** Rest of amino acids.

F. **<u>Imino and amino acids:</u>**

1. **Imino acids: Proline and hydroxyproline.**
2. **Amino acids:** Rest of amino acids.

G. **Sulfur and hydroxyl containing amino acids:**
   1. **Sulfer containing amino acids:** cysteine, cystine and methionine.
   2. **Hydroxyl containing amino acids: serine, threonine.**

## Nutritional classification of amino acids

They are classified into 3 main groups:

A. **Essential (indispensable) amino acids:**
   1. These are amino acids that cannot be formed in the body. They are ***essential to be taken in diet.***
   2. They are important for growth, health and protein synthesis.
   3. **They include:**
      *a)* Isoleucine.
      *b)* Leucine.
      *c)* Tryptophan.
      *d)* Methionine.
      *e)* Valine
      *f)* Threonine
      *g)* Lysine
      *h)* Phenylalanine

B. **Half (semi) essential amino acids:** These amino acids are formed in the body in amount enough for adults, but not for growing children. They include:
   *a)* Arginine.
   *b)* Histidine.

C. **Nonessential (dispensable) amino acids:** These are the rest of amino acids which are formed in the body, mostly formed from carbohydrate, in amount enough for adults and growing children.

| *I* | *Left* | *Home* | *To* | *MAke* |
|---|---|---|---|---|
| **Isoleucine** | **Leucine** | ***Histidine** | **Tryptophan** | **Methionine** |
| *Visit* | *Through* | *Libya* | *Philippine* | *Argentine* |
| **Valine** | **Threonine** | **Lysine** | **Phenyl-alanine** | ***Arginine** |

## Metabolic classification

Amino acids may be classified according to their metabolic fate in the body into pure ketogenic, pure glucogenic and both ketogenic and glucogenic amino acids.

A. **Ketogenic amino acids:** these give ketone bodies. **Leucine** is the only pure ketogenic amino acids.

B. **Glucogenic and ketogenic amino acids:** these give both ketone bodies and glucose. They are:
   1. **Phenylalanine.**
   2. **Tyrosine.**
   3. **Tryptophan.**

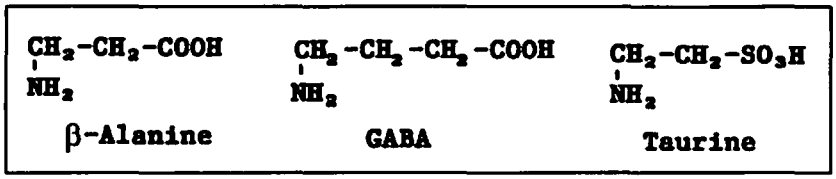
4. **Lysine.**
5. **Isoleucine.**

C. **Glucogenic amino acids:** these give glucose. They include the rest of amino acids not included in the 1st and 2nd groups.

## III. *Amino acids that do not enter in protein structure:*

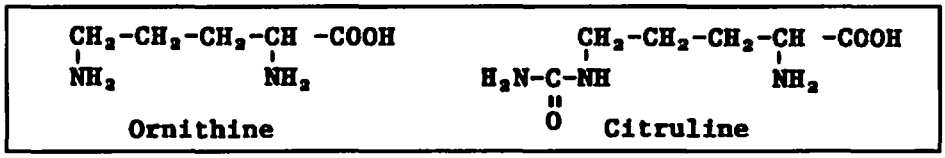
A. **Non alpha amino acids:** The amino group is not attached to α position. These amino acids perform important functions e.g.

1. **β-Alanine:** It enters in the structure of a vitamin called pantothenic acid (see chapter of vitamins).
2. **Gamma amino butyric acid (GABA):** This is a **neurotransmitter** formed from glutamate in brain tissue.
3. **Taurine:** This occurs in bile combined with bile acids.




B. **Amino acids which participate in urea cycle:** These are:

1. **Arginine** (α amino δ guanido valeric acid).
2. **Orinithin** (α,δ diamino valeric acid).
3. **Citruline** (α amino δ urido valeric acid).



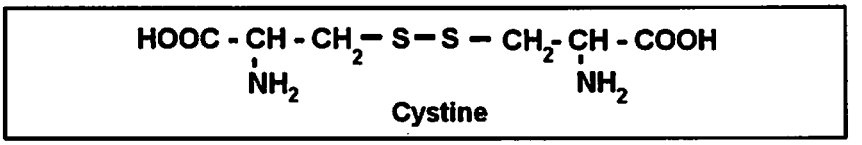

C. **Amino acids in intermediary metabolism:**

1. **Homoserine** (γ-Hydroxy α-amino butyric acid).
2. **Homocysteine** (γ-Thiol α-amino butyric acid).


D. **Amino acids containing iodine:** These are precursors of thyroid hormones:

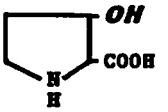
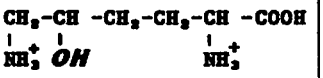
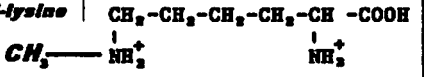
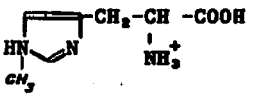
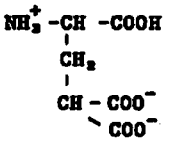
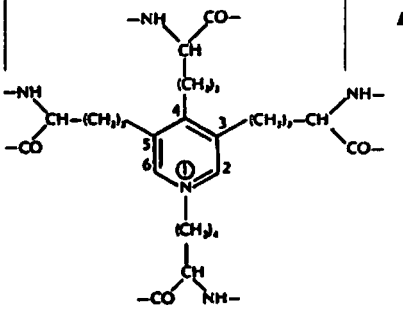
1. Monoiodotyrosine.
2. Diiodotyrosine.
3. Triiodotyrosine ($T_3$).
4. Tetraiodotyrosine ($T_4$).

**E. Cystine:** It is 2 molecules of cysteine (**dicysteine**) united together by removal of hydrogen of -SH groups. It is important for protein structure.



Cystine

## IV. *Amino acids found in proteins and formed post-translationally i.e. after protein synthesis:*

| Name | Structure | Source |
|---|---|---|
| *Hydroxyproline* |  | *Collagen and gelatin* |
| *Hydroxylysine* |  | *Collagen and gelatin* |
| *N-methyl-lysine* |  | *Fast muscle myosine* |
| *Methylhistidine* |  | *muscle myosine* |
| *γ Carboxyglutamate* |  | *Prothrombin and bone protein* |
| *Desmosine* |  | *Elastin* |

Each amino acid has a codon (sequence of 3 bases in DNA) that directs the translation and incorporation of that amino acid in protein. Some amino acids **accept groups or molecules after genetic translation (posttranslational modification)** e.g.:

| | | |
|---|---|---|
| Lysine | → | Hydroxylysine |
| Proline | → | Hydroxyproline |

## V. *Functions (biomedical importance) of amino acids:*

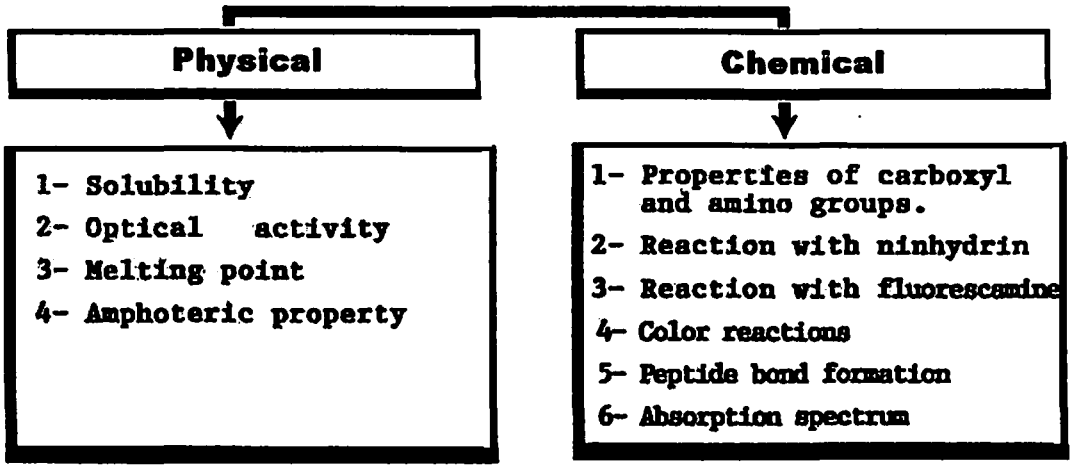
A. **Structural function**: Amino acids enter in the structure of:
   1. **Body peptides and proteins:** e.g. plasma proteins, tissue proteins, enzymes, etc.
   2. **Hormones:** some hormones are amino acid derivatives e.g. thyroxine and catecholamines.
   3. **Amines:** Some amino acids give corresponding amines by decarboxylation e.g. histidine gives histamine which is vasodilator.

B. **Neurotransmitters**: Some amino acids as glycine and glutamate act as neurotransmitters.

C. **Detoxication**: Some amino acids are used in detoxication reactions e.g. glycine.

D. **Health and growth**: Essential amino acids support growth in infants and maintain health in adults.

## VI. *Properties of amino acids:*




# *Physical properties:*

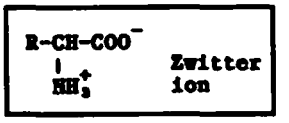
A. **Solubility**: Amino acids may be soluble in water, dilute acids, alkalies or ethanol.

B. **Optical activity**: All amino acids -except glycine- are optically active because they contain asymmetric carbon atom (=α-carbon).Thus they can rotate plane polarized light (see carbohydrate chemistry). Glycine contains no asymmetric carbon atom, so it is **optically inactive**.

C. **Melting point**: Amino acids are present in crystals with high ionic forces, stabilizing these crystals. So amino acids have high melting points above 200°C i.e. they are very stable molecules.

## D. Amphoteric properties and isoelectric point of amino acids:

1. **Amino acids are amphoteric molecules:** That is, they have both basic ($-NH_2$) and acidic (-COOH) groups.



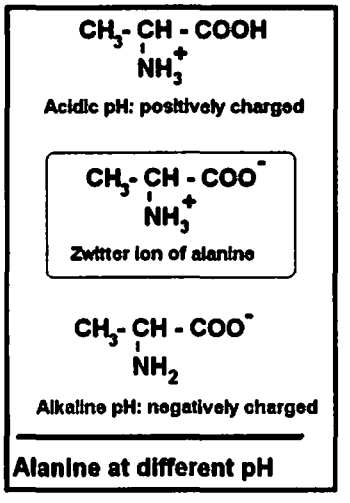

2. Monoamino-monocarboxylic acids exist in aqueous solutions as zwitter ions which means that they have both positive and negative charges.
   - *a)* The α-carboxyl group is dissociated and becomes negatively charged.
   - *b)* The α-amino group is protonated and becomes positively charged.
   - *c)* Thus the overall molecule is called zwitter ion.

**Definition of zwitter ion: It is the amino acid that carries both positive and negative charges. It is electrically neutral (=net charge is zero) and cannot migrate in electric field.**

- *d)* **Isoelectric pH (isoelectric point; PI): it is the pH at which the zwitter ion is formed.**
  1) Each amino acid has certain pH at which zwitter ion is formed.

$$PI = \frac{pK_1 + pK_2}{2}$$

  2) This pH is at midway between the pK values of the carboxyl and amino groups (see acid base balance).
  3) **Example: alanine**
     - i- **In strongly acidic pH** (at pH zero) alanine is present mainly in the form of **positively charged** molecule. Its pK ($pK_1$) = 2.34
     - ii- **By adding NaOH,** the carboxyl group loses its proton ($H^+$) and alanine carries both positive and negative charges **(zwitter ion).**
     - iii- **By adding more NaOH,** the solution becomes strongly alkaline, and the ammonium group ($-NH_3$) will lose its proton and alanine will become **negatively charged.** Its pK ($pK_2$) = 9.69.




     - iv- PI for alanine = $\frac{pK_1 + pK_2}{2}$

$$= \frac{2.34 + 9.69}{2} = 6.105$$

**∴Isoelectric point of alanine is 6.105 when alanine carries both positive and negative charges (zwitter ion).**

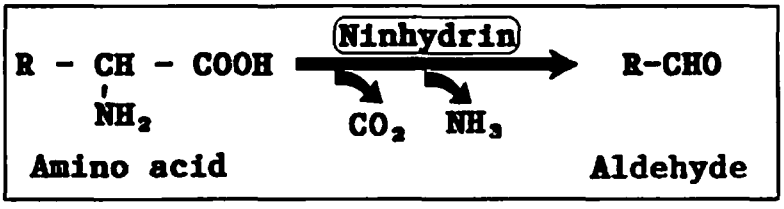
# *Chemical properties*

**A. Properties of carboxyl (-COOH) and amino ($-NH_2$) groups:**

1. Amino acids give all the reactions expected for the carboxyl and amino groups e.g. salt formation with acids and alkalies, decarboxylation, deamination, estrification, etc.

**B. Reaction with ninhydrin:**

1. Ninhydrin is a substance that reacts with amino acids to give $CO_2$, ammonia and aldehyde.




   *a)* Ninhydrin reacts with liberated ammonia to give **blue colour.**
   *b)* The intensity of the blue colour indicates the quantity of amino acids present. IT can detect as little as 1 ug of amino acids.
2. Ninhydrin reaction is given also by ammonia, peptides and proteins. It occurs with much slower rate without production of $CO_2$.
3. Ninhydrin can react with proline and hydroxyproline (imino group) but it gives yellow color.

**C. Reaction with fluorescamine:**

1. Like ninhydrin, fluorescamine forms a blue complex with amino acids.
2. It is more sensitive than ninhydrin, and can detect nanogram quantities of amino acids.

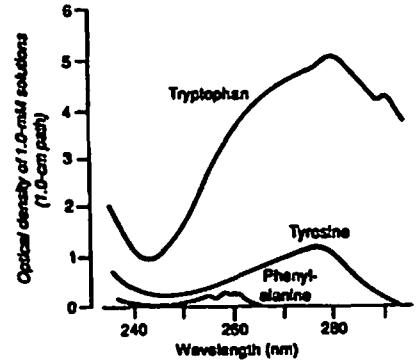
**D. Color reactions of amino acids:** These depend on the nature of radical (R),and give color products:

1. **Millon's reaction:** for tyrosine → Red color.
2. **Rosenheim's reaction:** for tryptophan → Purple color.
3. **Xanthoproteic reaction:** for phenylalanine and tyrosine → Orange color.

**E. Peptide bond formation:** Amino acids can react together to form peptide bond (see peptides).

**G. Absorption spectrum of amino acids:**

1. Amino acids are colorless. They do not absorb visible light.
2. Aromatic amino acids (particularly tryptophan) absorb ultraviolet light (wave length 250-290 nm).




The ultraviolet absorption spectra of tryptophan, tyrosine, and phenylalanine

# *Peptides*

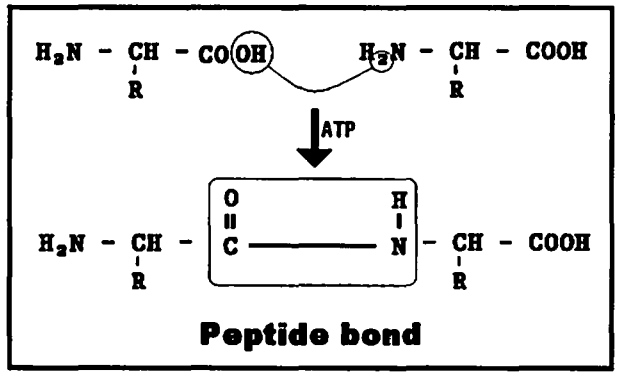
## I. *Definition:*

**A. Peptides are compounds, formed of *less than 50 amino acids* linked together by peptide bonds.**

1. **Dipeptide (2 amino acids and one peptide bond).**
2. **Tripeptide (3 amino acids and two peptide bonds).**
3. **Oligopeptide (3-10 amino acids).**
4. **Polypeptide (10-50 amino acids).**

**B. Peptide bond:**

1. It is a covalent bond formed between the carboxyl group of one amino acid and the α-amino group of another.
2. It is formed by removal of water.




**Peptide bond**

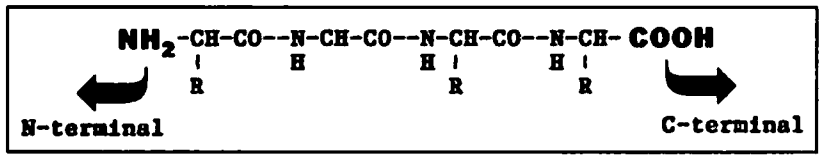
3. Peptide formation needs energy, getting from hydrolysis of a high energy phosphate compound e.g. **ATP.**
4. Peptide bond is semi-rigid bond i.e. no free rotation can occur around bond axis.

## II. *Primary structure of peptides:*

**A. It is the arrangement of amino acids in a peptide chain.**

**B. In a polypeptide chain, the N-terminal amino acid (i.e. the only amino acid that contains free amino group) is always to the left side. The C-**

**terminal** amino acid (i.e. the only amino acid that contains free carboxyl group) is always to the **right side.**




## III. *Separation of peptides:*

**A.** By electrophoresis.

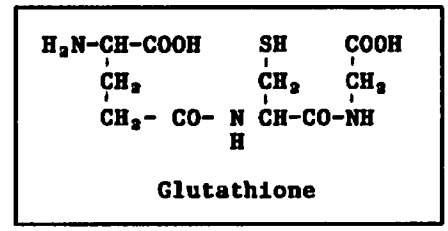
**B.** By exchange chromatography technique.

**IV.** ***Biologically active peptides:*** Peptides include many active compounds as hormones, neurotransmitters, neuromodulators, antibiotics, anti-tumour agents, aspartame and glutathione.

**A.** **<u>Hormones</u>:**

1. **Insulin and glucagon** from pancreas.
2. **Vasopressin and oxytocin** from posterior pituitary gland.
3. **ACTH** from anterior pituitary gland.

**B.** **<u>Glutathione</u>:**



Glutathione

1. It is a tripeptide formed of three amino acids: glutamate, cysteine and glycine.
2. It is also called glutamyl, cysteinylglycine.
3. Glutathione is commonly abbreviated as G-SH, where -SH indicates the sulfhydryl group of cysteine and it is the most active part of the molecule.
4. **Functions of glutathione:**
   - *a)* **Defence mechanism against certain toxic compounds (T):** Glutathione combine with them to produce non-toxic compounds.

     **T (toxic) + Glutathione → Non-toxic compound**
   - *b)* **Absorption of amino acids:** glutathione has a role in transport of amino acids across intestinal cell membrane.
   - *c)* Protect against cell damage and hemolysis of RBCs: Glutathione break down the hydrogen peroxide ($H_2O_2$) which causes cell damage and hemolysis.

     **$H_2O_2$ +Glutathione → $H_2O$ +oxidized glutathione**
   - *d)* **Activation of some enzymes.**
   - *e)* **Inactivation of insulin hormone.**

**C.** **<u>β-Lipotropin</u>:**

1. Is a polypeptide produced by anterior pituitary.
2. Is the precursor of β-endorphin:

*a)* β-endorphin acts as neurotransmitter and neuromodulator.

*b)* It has analgesic effect powerful 18-30 times than morphine.

D. **Bradykinin:**

1. It is released from specific plasma proteins by specific proteolytic enzyme.
2. It acts as a potent smooth muscle relaxant and produces vasodilatation and hypotension.

E. **Antibiotics**: e.g. valinomycin.

F. **Antitumor agent**: e.g. bleomycin.

G. **Aspartame:**

It is a dipeptide (aspartic acid and phenylalanine) that serves as sweetening agent. It is used in replacement of cane sugar.

H. **Atrial natriuretic peptide:**

1. It is a peptide produced by specialized cells in the heart and nervous tissue.
2. It stimulates the production of dilute urine (opposite to vassopressin).

# *Proteins*

## I. *Nature of proteins:*

A. **Composition:**

1. Proteins are macromolecules formed of amino acids united together by **peptide bonds.**
2. 20 Amino acids are commonly found in proteins, in different proportions.
3. Some proteins are formed of 2 or more polypeptide chains.

B. **Size of proteins:**

1. Proteins are molecules having a very high molecular weight, ranging from **5,000 to several millions.**
2. The term **protein** is applied to describe molecules greater than **50 amino acids.**
3. Molecules contain less than 50 amino acids are termed: **peptides.**

## II. *Functions of proteins:*

A. **Enzymes**: Enzymes are proteins.

B. **Transport**: Of small molecules and ions e.g.

1. Hemoglobin is a carrier for oxygen.
2. Lipids are transported as lipoproteins.

C. **Structural elements**: e.g.
   1. **Cell membrane** contains proteins in the form of **glycoproteins.**
   2. **Skin and bone:** e.g. contains proteins in the form of **collagen.**

D. **Hormonal regulation**:
   1. Some **hormones** are protein in nature e.g. growth hormone.
   2. Cellular **receptors** that recognise hormones are proteins.

E. **Defence mechanism**:
   1. **Antibodies** (immunoglobulins) are protein in nature.
   2. **Keratin** found in skin and other tissues is protein that protect against mechanical and chemical injury.

F. **Blood clotting**: Coagulation factors are proteins.

G. **Storage**: as ferritin which is a storage form of iron.

H. **Control of genetic expression**: many regulators of genes are protein in nature.

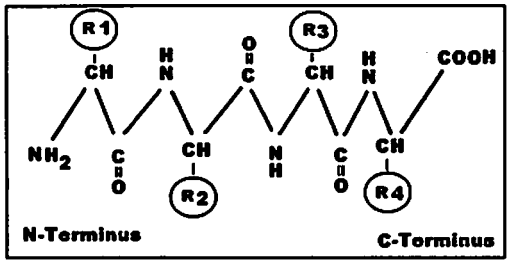
## III. *Conformation of proteins = (protein structure):*

Every protein in its native state has a 3 dimensional structure (primary, secondary and tertiary) which is known as conformation. **Conformation** is essential for the functions of each protein. Any change in protein conformation may lead to a disease. Proteins which are formed of more than one peptide chain have additional quaternary structure.

A. **Primary structure**:

***It is the arrangement of amino acids in the polypeptide chain.*** The peptide bonds are covalent bonds responsible for the primary structure.

1. Each polypeptide chain starts on the left side by free amino group of the first amino acid. It is termed **N-terminal** (or N-terminus) amino acid.
2. Each polypeptide chain ends on the right side by free carboxyl group of last amino acid. It is termed **C-Terminal** (or C-terminus) amino acid.



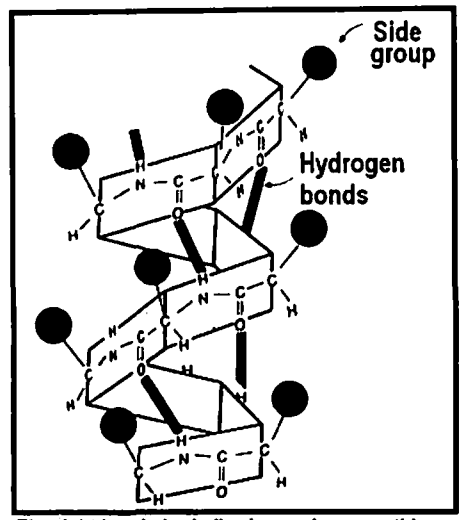

3. The remaining amino acids in the chains are termed: **amino acid residues.**
4. The types and arrangement of amino acids in each protein is determined by the genetic information present in **DNA.**

B. **Secondary structure**:

***It is the spatial relationship of adjacent amino acid residues.***

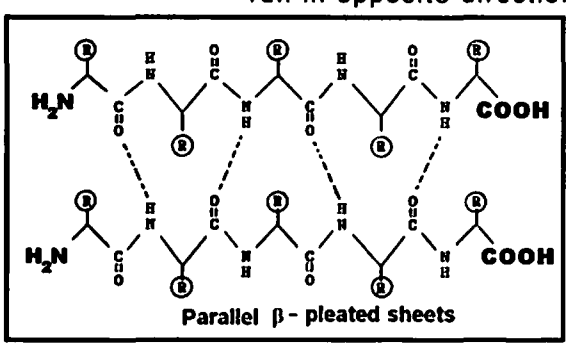
1. Secondary structure results from interaction of adjacent amino acid residues (first and fourth).

2. **Hydrogen bonds** are responsible for secondary structure. It is the bond between the hydrogen of **-NH group** of one amino acid residues and the carbonyl oxygen **(C=O)** of the fourth one.
3. There are 2 main forms of secondary structure;α-helix and β-pleated sheets.
4. **The α-helix:**
   *a)* It is a rod like structure with the peptide bonds coiled tightly inside and the side chains of the residues (R) extending outward from the chain.
   *b)* **Characteristics:**
      1) Each (C=O) of one amino acid is hydrogen bonded to the (-NH) of the next fourth amino acid in the chain (1 → 4).
      2) The complete turn distance equals **54 nm.**
      3) Each turn contains **3.6 amino acids residues.**

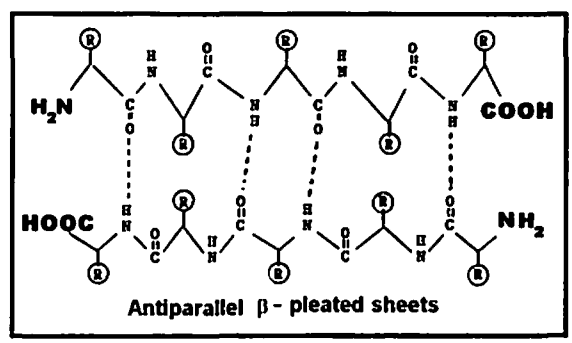


The right-handed α-helix shows planar peptide bonds and hydrogen bonds between every fourth bond.

5. **β-pleated sheets:**
   *a)* This structure is formed between two or more separate polypeptide chains. It may also be formed between segments of the same polypeptide chain.
   *b)* Hydrogen bond is also respónsible for its formation. It occurs between (-NH) group of one chain (or segment) and (C=O) group of adjacent chain (or segment).
   *c)* Two types of β-sheets are present:
      1) **Parallel β-sheets:** in which the two polypeptide chains run in the same direction.
      2) **Antiparallel β-sheets:** in which the two polypeptide chains run in opposite direction.



Parallel β - pleated sheets

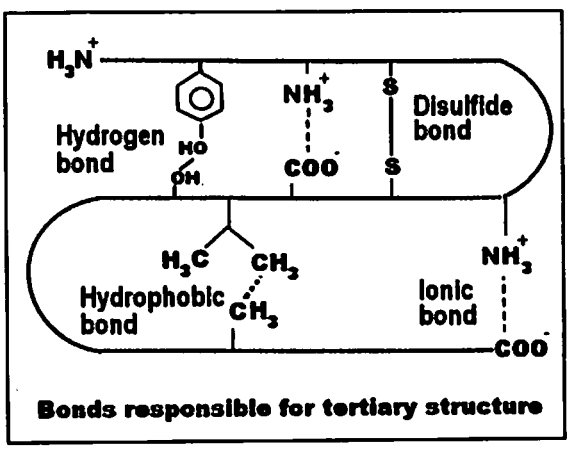


Antiparallel β - pleated sheets

**C. <u>Tertiary structure</u>:** This is the final arrangement of a single polypeptide chain resulting from spatial relationship of more distant amino acid residues.

1. There are two forms of tertiary structures:
   - *a)* **Fibrous:** which is an extended form e.g. α-keratin, collagen and elastin.
   - *b)* **Globular:** which is a compact form and results from folding of polypeptide chain e.g. myoglobin.

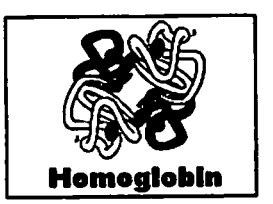

2. **Bonds responsible for tertiary structure are:**
   - *a)* **Hydrogen bonds:** within the chain or between chains.
   - *b)* **Hydrophobic bonds:** between the nonpolar side chains (R) of neutral amino acids.
   - *c)* **Electrostatic bonds** (salt bonds):between oppositely charged groups in the side chains of amino acids e.g. Σ-amino group of lysine and carboxyl group of aspartate.
   - *d)* **Disulfide bonds:** between cysteine residues within the chain.



**Bonds responsible for tertiary structure**

**D. <u>Quaternary structure</u>:** Many proteins are composed of several polypeptide chains. Each polypeptide chain is called: **subunit.**

1. Each subunit has its own primary, secondary and tertiary structure.
2. **Bonds responsible for quaternary structure:**
   - *a)* Hydrogen bond.
   - *b)* Hydrophobic bond.
   - *c)* Electrostatic bond
3. **Example of proteins having quaternary structure:**
   - *a)* Insulin: 2 subunits.
   - *b)* Lactate dehydrogenase enzyme: 4 subunits.
   - *c)* Globin of hemoglobin: 4 subunits.


**Hemoglobin**

## E. Summary of protein structure:

1. **Primary structure:**
   a. It is the arrangement and number of amino acids that enter in the structure of protein.
   **b.** Peptide bonds are covalent bonds responsible for primary structure.

2. **Secondary structure:**
   a. It is spatial relationship of adjacent amino acid residues (first and fourth). They are 2 forms: α-helix or β-pleated sheets.
   b. Hydrogen bonds are responsible for secondary structure

3. **Tertiary structure:**
   a. It is the spatial relationship of more distant amino acid residues.
   b. Hydrogen, hydrophobic, electrostatic and disulfide bonds are responsible for tertiary structure.
   **c.** There are 2 forms of tertiary structure: fibrous (extended) and globular (compact) form.

4. **Quaternary structure:**
   a. It is the arrangement of proteins having more than one subunit.
   **b.** Hydrogen, electrostatic and hydrophobic bonds are responsible for quaternary structure.

5. **Bonds responsible for protein structure:**
   Protein structure is generally stabilized by 2 strong covalent bonds and 3 weak noncovalent bonds:
   a. **Covalent bonds**: peptide bond disulfide bond.
   **b. Noncovalent bonds**: hydrogen, hydrophobic and electrostatic bonds.

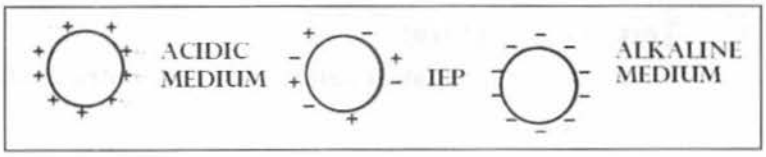
## IV. *Properties of proteins:*

### A. Solubility:

1. Some proteins are soluble in water e.g. albumin.
2. Some proteins are soluble in salt solution e.g. globulin.
3. Some proteins are soluble in alcohol e.g. protamine.
4. Some proteins are insoluble at all e.g. scleroproteins.

**B. Amphoteric properties:**

1. Proteins contain **free amino group (N-terminal)** and contain also free amino groups of basic amino acids.
2. Proteins contain **free carboxylic group (C-terminal)** and contain also free carboxylic group of acidic amino acid.
3. The presence of both free amino and carboxyl groups make the protein **amphoteric** compound and it can act as a buffer.
4. Proteins are positively charged in acidic medium and negatively charged in alkaline medium.
5. **Isoelectric point (I.E.P.):** It is the **pH** at which the protein molecule carries equal positive and negative charges. It is electrically neutral, least soluble and does not migrate in electric field.



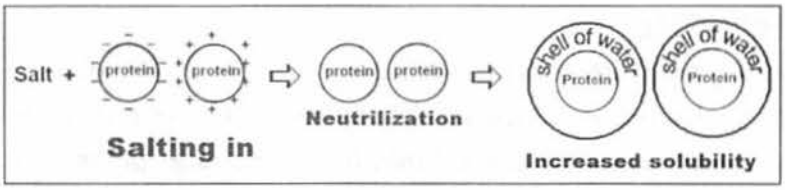

**C. Color reactions:** All the color reactions of amino acids can be given by proteins that contain those amino acids:

1. **Roseinheim's reaction:** purple ring given by proteins containing **tryptophan.**
2. **Xanthoproteic reaction:** orange color is given by proteins containing **phenylalanine** and **tyrosine.**
3. **Millon's reaction:** Red color is given by proteins containing phenolic (-OH) group of **tyrosine.**
4. **Sulphur reaction:** black or grey color is given by proteins containing **sulphur amino acids (cysteine).**
5. **Biuret's test:**
   *a)* This is a **general test for all proteins** because it is given by peptide linkage (-CO-NH-).
   *b)* The reaction occurs between protein, sodium hydroxide and copper sulphate giving violet complex.

***Protein (-CO-NH-) + NaOH + $CuSO_4$ → Violet complex***

**D. Salting in and salting out:**

1. **Salting in:** means increase solubility of a substance by adding small amounts of salts.



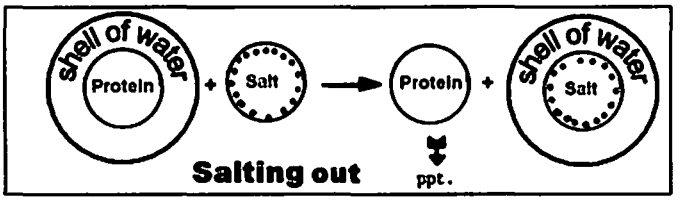
*a)* Globulin is insoluble in water. Addition of small amount of ammonium sulphate increases its solubility.

*b)* Salting in occurs due to binding of salt ions with the ionizable groups of protein. This decreases the interaction between oppositely charged groups on the protein molecules. Water molecules are then able to form a layer around these molecules.

2. **Salting out:** means precipitation of proteins by adding large amount of salts.

*a)* Globulin is precipitated by adding 50% saturated ammonium sulfate solution.

*b)* Large number of salt ions competes with the protein for water molecules.




E. **Precipitation of proteins:** This can be done by:

1. **Various concentrations of salt solutions:** Salting out.
2. **Various concentrations of alcohol.**
3. **By heavy metals** e.g. mercury, silver. Heavy metals combine with proteins forming insoluble metalproteins.
4. **By alkaloidal reagents** e.g. trichloroacetic acid and picric acid. Alkaloidal reagents form insoluble complex with proteins.

## IV. *Denaturation of proteins:*

A. **Definition:** Protein denaturation means unfolding and loss of secondary, tertiary and quaternary structure.

1. Denaturation does not affect primary structure i.e. not accompanied by hydrolysis of peptide bonds.
2. Denaturation may be reversible (in rare cases).

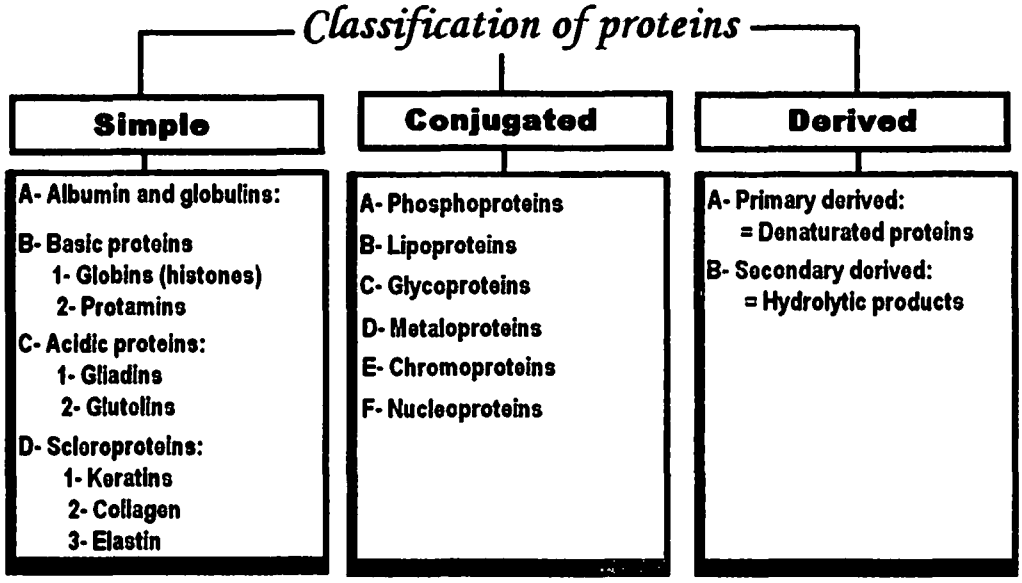
B. **Effect of protein denaturation:**

1. **Loss of biological activity:** e.g. insulin loses its activity after denaturation.
2. Denaturated proteins are often **insoluble.**
3. Denaturated proteins are easily **precipitated.**

C. **Causes of denaturation:**

1. **Heat:** causes coagulation and precipitation of certain proteins like albumin.

2. **Organic solvents:** They interfere with hydrophobic bonds of proteins.
3. **Detergents:** They contain both hydrophobic and hydrophilic groups i.e. **amphipathic**. They interfere with hydrophobic bonds of proteins.
4. **Mechanical mixing:** As stirring and grinding of proteins.
5. **Strong acids or bases:** They lead to change in pH which affects the charges on polypeptide chains. As a result, hydrogen and electrostatic bonds will be disrupted.
6. **Heavy metals:** as lead and mercury salts:
   *a)* They form ionic bonds with negatively charged ions in polypeptide chains. This leads to disruption of electrostatic bonds.
   *b)* They unite with **-SH (sulfhydryl)** groups of proteins causing its denaturation(**-S-Hg**).
7. **Alkaloidal reagents:** as trichloroacetic acid and picric acid. They cause precipitation of proteins.
8. **Enzymes:** e.g. Digestive enzymes.
9. **Urea, ammonium sulphate and sodium chloride:** They cause precipitation of proteins.
10. **Repeated freezing and thawing:** cause disruption of hydrogen and other weak bonds.




I. ***Introduction:*** Proteins are classified into 3 groups:

A. **Simple proteins**: On hydrolysis they give amino acids only.

B. **Conjugated proteins**: On hydrolysis they give amino acids and non-protein groups (prosthetic groups).

C. **Derived proteins:**

1. **Primary derived proteins** they include denaturated proteins.
2. **Secondary derived proteins:** they include products of hydrolysis of simple and conjugated proteins.

## II. *Simple proteins:*

### A. Albumin and globulins:

1. Both are coagulated by heat.
2. Both are proteins of high biological value i.e. contain all essential amino acids and easily digested.
3. Both are almost present in the same sources: blood, milk and egg.
4. ***The differences between them can be shown in the following table:***

| | Albumin | Globulins |
|---|---|---|
| **Coagulation by heat:** | Coagulable | Same |
| **Biological value:** | Protein of high biological value | Same |
| **Solubility:** | Soluble in water | Soluble in salt solution |
| **Molecular weight:** | 68,000 | 150,000 |
| **Precipitation:** | By full saturated ammonium sulphate | By half saturated ammonium sulphate |
| **Sources:**<br>**1)Blood**<br>**2)Milk**<br>**3)Egg** | <br>Serum albumin<br>Lactalbumin<br>Egg albumin | <br>Serum globulins<br>Lactglobulin<br>Egg globulin |

### B. Globins (=histones) and protamines:

1. Both are basic proteins i.e. rich in basic amino acids.
2. ***The differences between them are:***

| | Globins (histones) | Protamine |
|---|---|---|
| **Type of basic amino acid** | Histidine | Lysine and arginine |
| **Solubility** | In salt solution | 1. In salt solution<br>2. In 70% ethanol |
| **Sources:** | 1. Combined with DNA to form nucleoproteins.<br>2. Combined with heme to form hemoglobin | In fish, combined with DNA to form nucleoprotein. |

### C. Gliadins and glutelins:

1. Both are acidic proteins i.e. rich in acidic amino acids: glutamic acid.

2. Both are present in cereals.
3. Both are soluble in diluted acids and alkalies. Gliadins also soluble in 70% ethanol.

## D. Scleroproteins:

They include: keratin, collagen, elastin and reticulin.

### 1. α-Keratins:

*a)* **Location:** They are found in hair, nail, enamel of teeth and outer layer of skin.

*b)* **Structure:** They are α-helical polypeptide chains. They are rich in cysteine (which provides disulfide bonds between adjacent polypeptide chains).

*c)* **Functions:** Keratin is a tough fibrous protein that strengthens skin, hair and nails with its tight strands.

*d)* **Solubility:** It is insoluble due to their high content of hydrophobic amino acids.

### 2. Collagens:

*a)* **Types of collagens:**

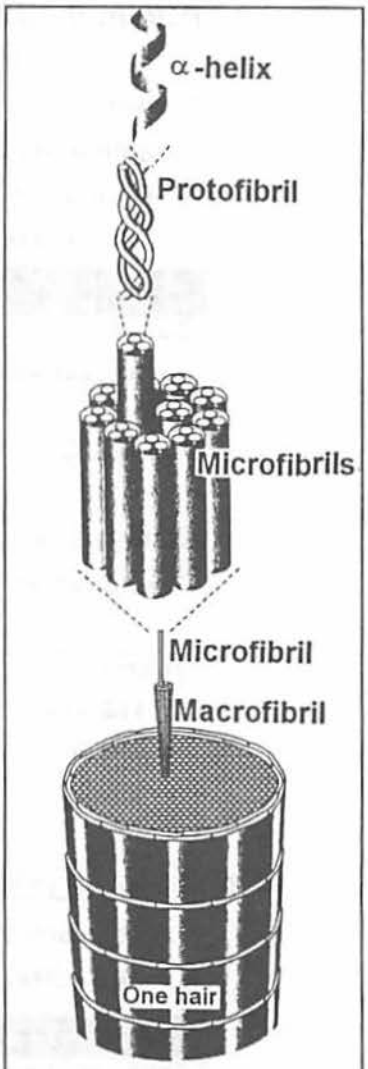
1) There are more than 12 types of collagen. IN human body type I constitute 90% of cell collagens.
2) Collagens form about **30% of total body proteins.**

*b)* **Location:**

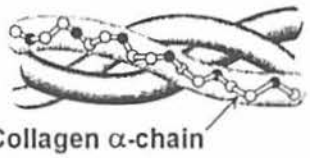
1) It is the protein of connective tissue present in skin, bones, tendons and blood vessels.
2) Collagen may be present as a gel e.g. in extracellular matrix or in vitreous humour of the eye.

*c)* **Functions:**

1) Collagen provides the framework for various organs such as the kidneys and lymph nodes.
2) Collagen also gives great support and strength to structures such as the bones, tendons and blood vessels.




Structure of hair




Triple - stranded helix of collagen.

*d)* **Structure of collagen:**

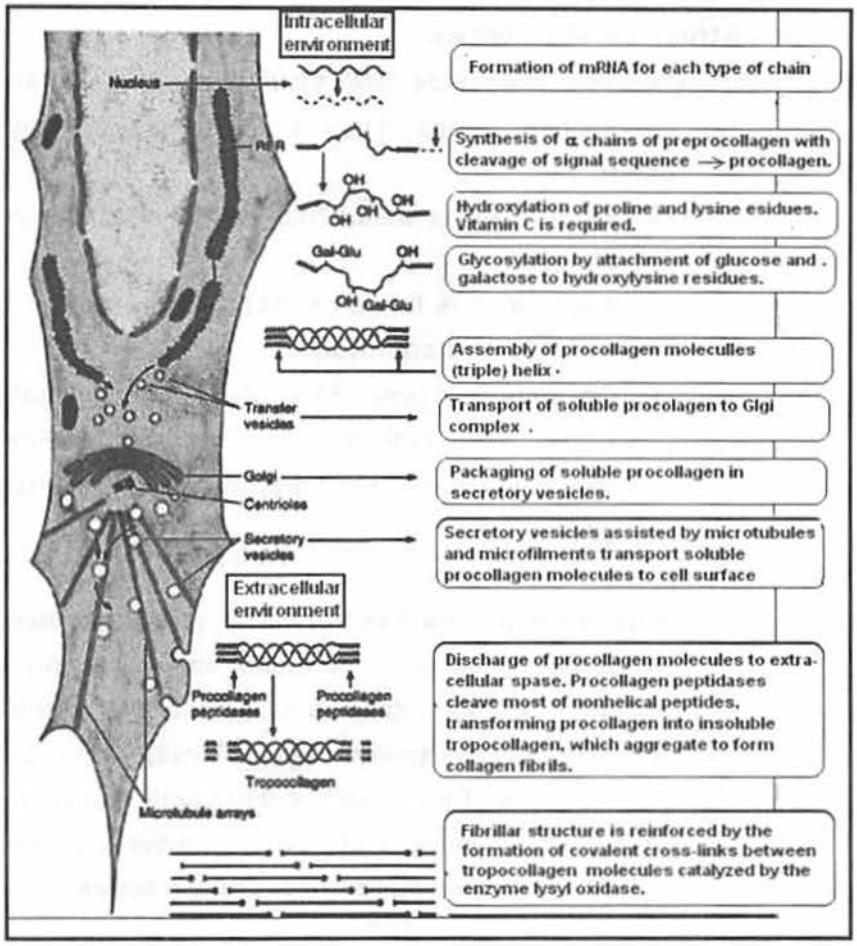
1) Collagen molecules are simple protein, consist of 3 α polypeptide chains. They are held together by hydrogen bonds.
   - i- Each chain is about **300 nm** in length and 1.5 nm in diameter.
   - ii- Each chain is formed of **1050 amino acids**.
2) **Amino acids composition:**
   - i- Collagen contains 33% glycine (the smallest amino acid), 10% proline, 10% hydroxy proline and 1% hydroxylysine. Every third amino acid in the α-chain is glycine.

*e)* **Collagen molecule has very firm structure due to:**

- i- Each helical turn contains only 3 amino acids. For other proteins, each turn contains 3.6 amino acids.
- ii- Glycine (the smallest amino acid) forms 33% of total molecule. This make the polypeptide chains compact.
- iii- The high content of hydroxyproline and hydroxylysine increase the number of hydrogen bonds.

*f)* **Collagen synthesis:**

1) Collagens are formed by connective tissue cells called fibroblasts.
2) **Intracellular location:** The polypeptide chains of preprocollagen are synthesized on the rough endoplasmic reticulum, where preprocollagen is cleaved → Procollagen + Signal (pre) sequence.
3) **Proline and lysine residues are hydroxylated** by a reaction that requires $O_2$ and vitamin C.
4) **Glycosylation:** by glucose and galactose that added to hydroxylysine residues.
5) The procollagen (in the form of triple helix) is secreted from the cell and cleaved → **Collagen.**
6) **Cross links** are produced.




*g)* **Solubility and denaturation:**

1) **Solubility:** Collagen is insoluble in all solvents. It is protein of low biological value and not digestible.

2) **Denaturation:**

i- When collagen is heated, it loses all of its structure. The triple helix unwinds and the chains are separated. Then when this denaturated mass cools down, it soaks up all the surrounding water like sponge, forming gelatin.

ii- **Gelatin** is soluble in water and digestible. Gelatine is given for patients during convalescence (in the form of jelly).

*h)* **Collagen diseases: (Scurvy):**

i- It is due to a deficiency in ascorbic acid (vitamin C). See vitamins.

**3. Elastin:**

*a)* **Characters:**

It is connective tissue protein. It is **rubber like** i.e. it can be stretched to several times as their normal length, but

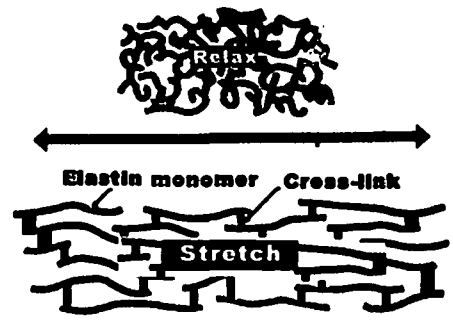
recoil to their original shape when the stretching force is relaxed.

*b)* **Location:**

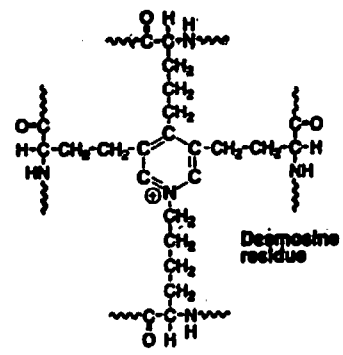
It is present in lungs, the walls of large blood vessels and elastic ligaments.

*c)* **Structure:**

1) Elastin is formed of 4 polypeptide chains.
2) Elastin is similar to collagen, being rich in glycine (1/3 of its amino acids) and proline. It is poor in hydroxyproline and hydroxylysine.
3) The 4 polypeptide chains are interconnected through their lysine residues. The 4 lysine residues are linked together to form a cyclic structure termed: **desmosine.**
4) Elastin is capable of undergoing 2 way stretch, due to its content of desmosine.




**Elastin fibers in relaxed and stretched conformation**




Desmosine cross-link elastin.

*d)* **Functions:**

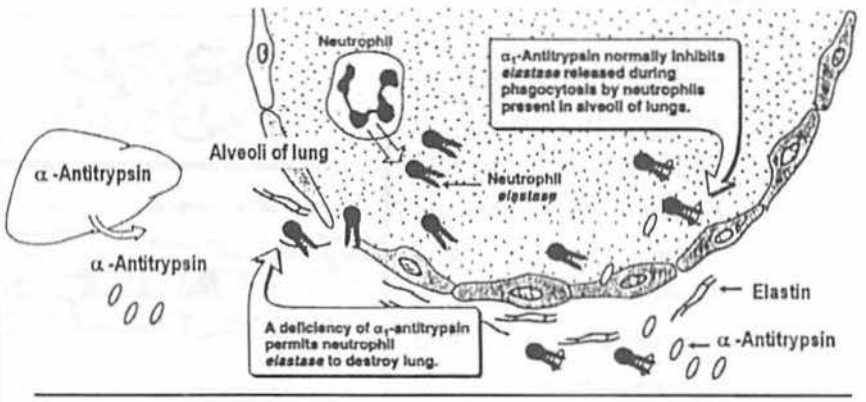
**Elastin is a protein that coil and recoils like a spring within the elastic fibers of connective tissue and accounts for the elasticity of structures such the lungs, blood vessels and ligaments.**

*e)* **Role of $\alpha_1$-antitrypsin ($\alpha_1$-AT) in elastin degradation:**

1) **$\alpha_1$-antitrypsin is an enzyme produced mainly by liver. It is also produced by blood cells monocytes and macrophages.**
2) **It is present in blood and other body fluids.**
3) **It inhibits a number of enzymes and destroys proteins.**
4) **Role of $\alpha_1$-AT in the lungs: In the normal lung, the alveoli are exposed to low levels of elastase enzyme released from neutrophils. Their proteolytic activity can destroy the**

elastin in alveolar walls. This elastase enzyme activity is inhibited by $\alpha_1$-antitrypsin.

5) **Deficiency of $\alpha_1$-AT:** Leads to destruction of connective tissue of alveolar walls by neutrophils elastase. This leads to lung disease called: **emphysema.**




Destruction of alveolar tissue by elastase released from neutrophils.

**Comparison between collagen and elastin:**

| | Collagen | Elastin |
|---|---|---|
| **Number of chains** | 3 | 4 |
| **Amino acids** | 1/3 glycine, rich in proline, more hydroxyproline, | 1/3 glycine, rich in proline, less hydroxyproline and free from hydroxylysine |
| **Structure** | Fibrous | *Fibrous in extended form<br>*Globular in relaxed form |
| **Direction of stretch** | One direction | 2 Directions due to presence of desmosine |

**Summary of solubility properties of simple proteins:**

| | $H_2O$ | Salt (saline) | Dilute acids | Dilute alkalies | 70% ethanol |
|---|---|---|---|---|---|
| **1-Albumin& globulin** | **Soluble** | **Soluble** | **Soluble** | **Soluble** | ***Insoluble*** |
| **2-Globin (histone)** | **Soluble** | **Soluble** | **Soluble** | **Soluble** | ***Insoluble*** |
| **3-Protamine** | **Soluble** | **Soluble** | **Soluble** | **Soluble** | **Soluble** |
| **4-Gliadine** | ***Insoluble*** | ***Insoluble*** | **Soluble** | **Soluble** | **Soluble** |
| **5-Glutelins** | ***Insoluble*** | ***Insoluble*** | **Soluble** | **Soluble** | ***Insoluble*** |
| **6-Scleroproteins** | ***Insoluble*** | ***Insoluble*** | ***Insoluble*** | ***Insoluble*** | ***Insoluble*** |

## III. *Conjugated proteins:*

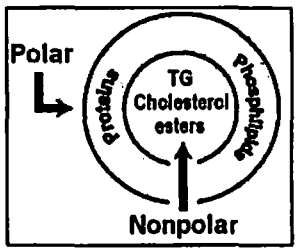
On hydrolysis, they give protein part **(apoprotein)** and nonprotein part **(prosthetic group).** They include:

## A. Phosphoproteins:

1. These are proteins conjugated with phosphate group.
2. Phosphate is attached to -OH group of serine **(phospho-serine)** or threonine **(phosphothreonine)** present in protein part.
3. **Examples:**
   *a)* **Casein:** A milk protein .
   *b)* **Vitellin :**Present in egg yolk.
   *c)* **Phosphoenzyme:** Phosphorylation (addition of phosphate to an enzyme) may activate or inactivate enzyme according to its type.

## B. Lipoproteins:

1. These are proteins conjugated with lipids.
2. **Example:** Plasma lipoproteins.
3. Lipoproteins are formed of water insoluble central core formed of triacylglycerols and cholesterol esters surrounded by a water soluble layer formed of protein part (apolipoprotein) and phospholipids.




4. **Importance of lipoproteins structure:**
   *a)* Helps water insoluble lipids to transport in blood.
   *b)* Helps water insoluble substances to pass through cell membranes.

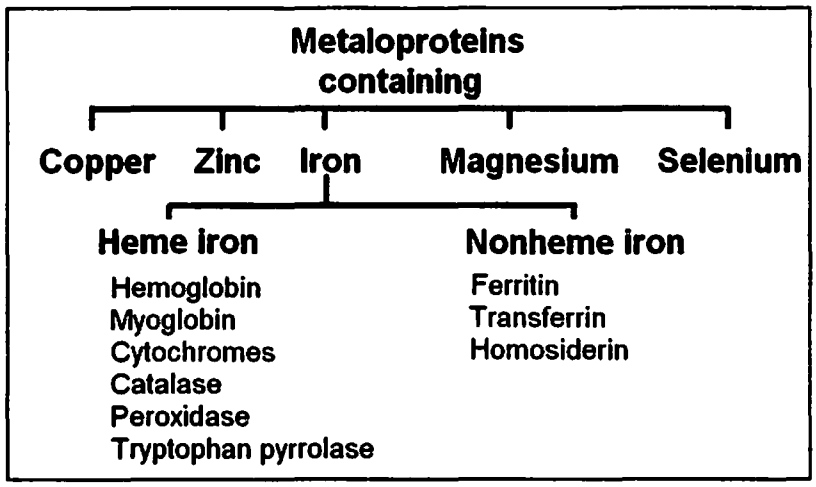
## C. Glycoproteins and proteoglycans:

1. These are proteins conjugated with carbohydrates in varying amounts. Glycoproteins contain short branched chain of sugar units (2-15 units). Proteoglycans contain long unbranched chains of sugar units (more than 50 units).
2. **Examples:**
   *a)* **Glycoproteins:** Blood group-enzymes and mucin.
   *b)* **proteoglycans:** Cell membranes.
   Note: For details: see carbohydrate chemistry.

## D. Nucleoproteins:

1. These are proteins (protamines or histones) conjugated with nucleic acids (DNA or RNA).
2. **Examples:**
   *a)* **Chromosomes:** These are proteins conjugated with DNA.
   *b)* **Ribosomes:** These are proteins conjugated with RNA.

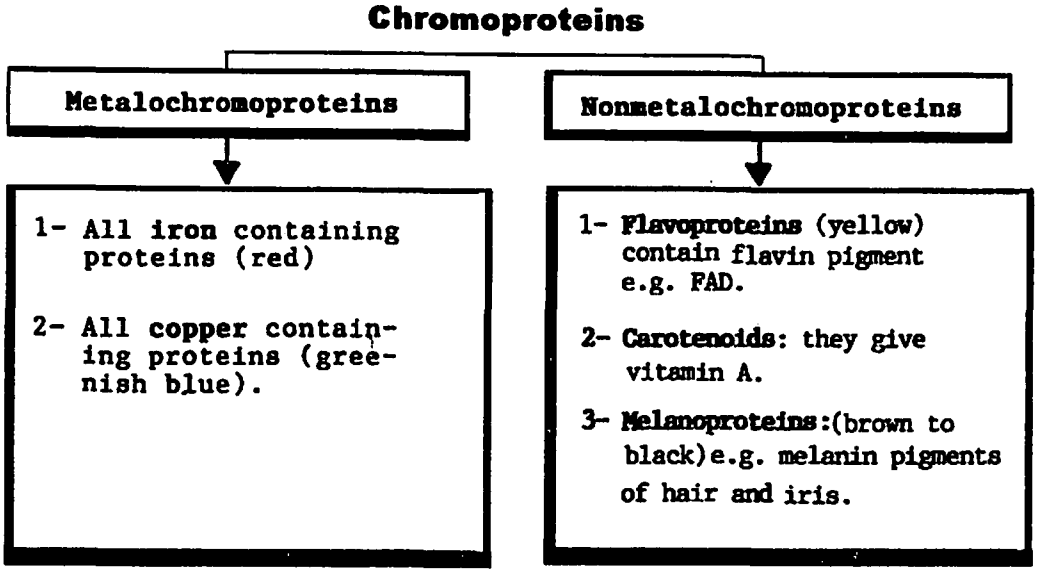
**E. Metaloproteins:** These are proteins conjugated with metals.



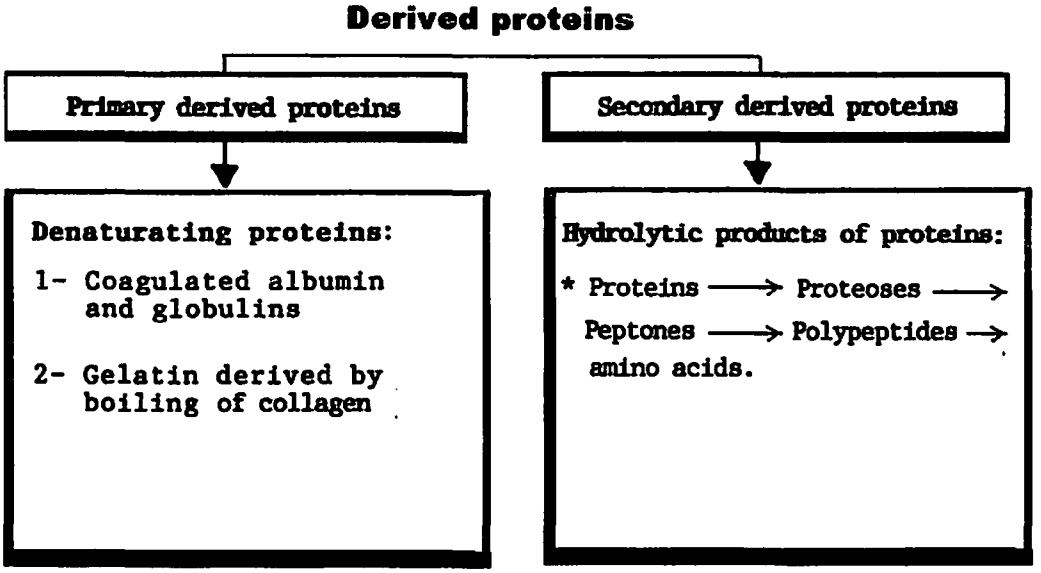

1. According to the type of metal, they are classified into:
   - *a)* **Metaloproteins containing iron:** The iron may be in the form of heme or nonheme iron:
     1) **Heme iron:**
        - i- Hemoglobin, myoglobin, and some enzymes as cytochromes, catalase, peroxidase, tryptophan pyrrolase).
     2) **Nonheme iron:**
        - i- **Ferritin:** Is the storage form of iron, present in liver, spleen, bone marrow and intestinal cells.
        - ii- **Transferrin:** Is the iron carrier protein in the plasma.
        - iii- **Hemosedrin:** Formed as a result of iron toxicity (over dosage)as in case of repeated blood transfusion.
   - *b)* **Metaloproteins containing copper:**
     1) **Ceruloplasmin:** Is plasma protein, responsible for the oxidation of ferrous ions ($Fe^{++}$) into ferric ions ($Fe^{+++}$).
     2) **Erythrocuprein:** Present in red cells.
     3) **Hepatocuprein:** Present in liver.
     4) **Cerebrocuprein:** Present in brain.
     5) **Oxidase enzymes:** Contain cupper e.g. cytochrome oxidase.
   - *c)* **Metaloproteins containing zinc:**
     1) **Insulin** hormone.
     2) **Some enzymes** e.g. carbonic anhydrase.
   - *d)* **Metaloproteins containing magnesium:**
     1) Some enzymes as kinase and phosphatase.
   - *e)* **Metaloproteins containing selenium:**
     1) Glutathione peroxidase.

**F. Chromoproteins:**

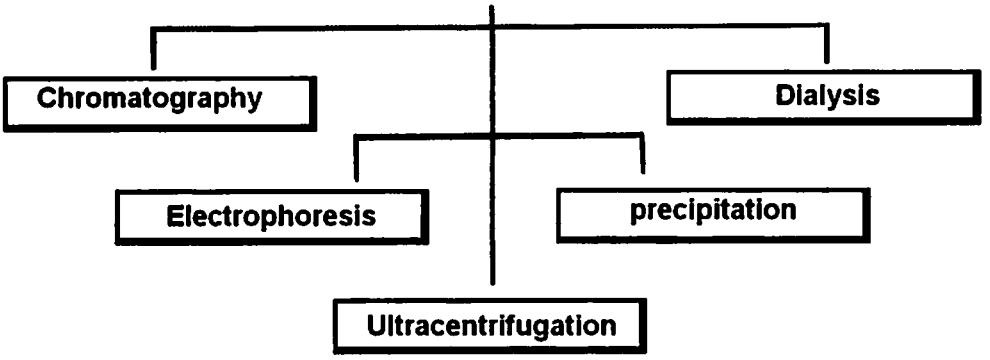
1. They are proteins conjugated with colored elements.
2. They are divided into metalochromoproteins (contain colored metal) or non-metalochromoproteins (contain colored pigment).




## IV. *Derived proteins:*



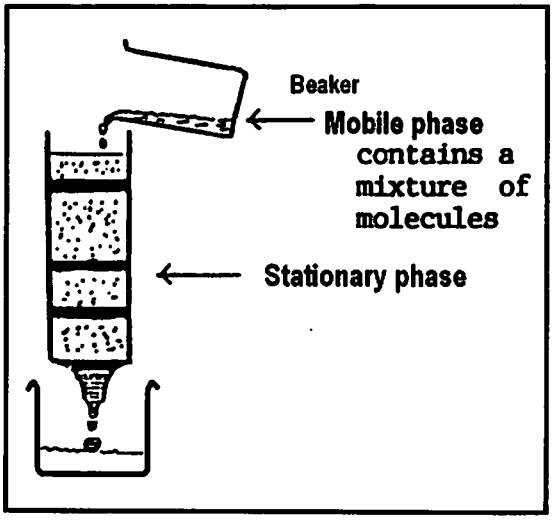
# Techniques for Separation of Proteins and Amino Acids




## I. *Chromatography:*

### A. Definition:

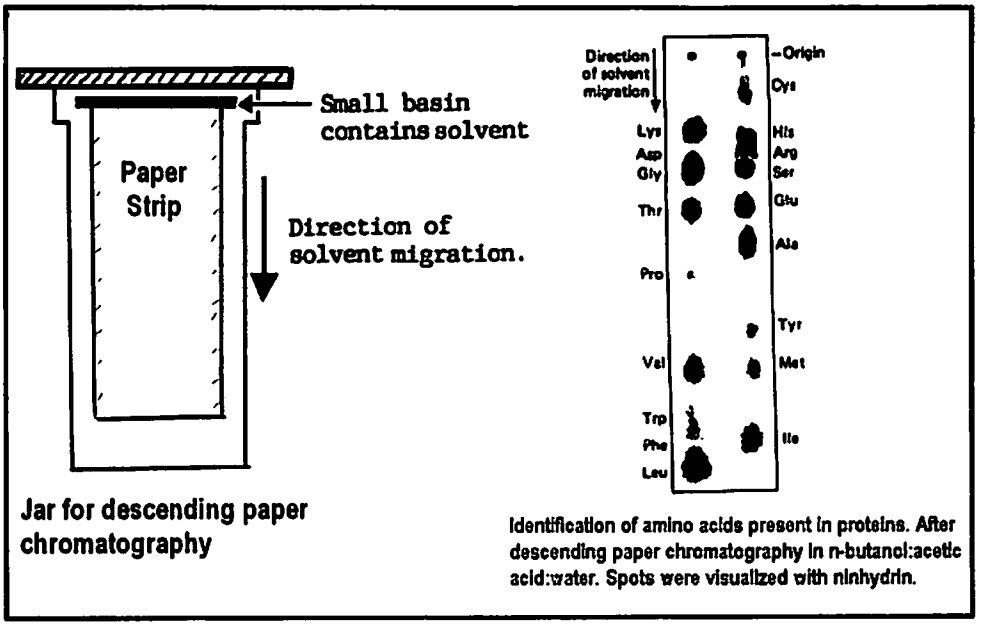
1. Chromatography is a group of separation techniques, where a mixture of molecules is separated into its components.
2. The separated molecules are divided between a **stationary** and **mobile** phases.
3. The separation process depends on the tendency of one type of molecules in the mixture to associate more strongly with one phase than the other.




### B. Types of chromatography:

1. **Paper chromatography:** for separation of amino acids. Its **procedure** is as follows:
   - *a)* A strip of a filter paper (made of **cellulose**) is marked with a pencil about 5 cm from one end.
   - *b)* Samples of amino acid solutions are applied at different points on the marked line.
   - *c)* The strip is then suspended in a sealed vessel that contains the chromatographic solvents.
   - *d)* **The solvents** are polar mixtures of water, alcohols and acids or bases. **The more polar** components of the solvent associate

with the cellulose and form a **stationary phase. The less polar** components constitute the **mobile phase.**




Identification of amino acids present in proteins. After descending paper chromatography in n-butanol:acetic acid:water. Spots were visualized with ninhydrin.

*e)* The solvent migrates **down** the paper (hence its name: **descending chromatography).** When the solvent almost reaches to the end, the strip is dried and treated with **0. 5% ninhydrin** in acetone followed by heating at 90-110 °C for few minutes.

1) Amino acids with large nonpolar side chains (as leucine and isoleucine) migrate more quickly than those with short nonpolar side chains (as threonine and serine).
2) This means that **polar amino acids** are associated with **hydrophilic stationary phase** and **nonpolar amino acids** are associated with **mobile organic solvent.**

*f)* The ratio of the **distance travelled** by an **amino acid** to that travelled by the solvent front, both measured from the marked point of application of the amino acid mixture is called the **$R_f$ value** for the amino acid. By knowing **$R_f$** values of different amino acids we can identify unknown amino acids.

*g)* **Quantitation of amino acids** may performed by cutting out each spot eluting with suitable solvent, and performing a quantitative colorimetric (ninhydrin) analysis.

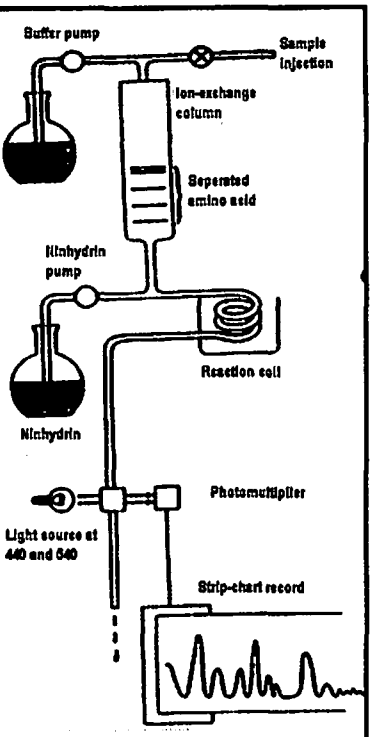
*h)* In paper chromatography, the solvent may be placed in base of the apparatus to be migrated **upwards** and this type is called: **ascending chromatography.**

**2. Thin layer chromatography(TLC):**

The same principle as that of paper chromatography but the stationary phase is made of silica jell or cellulose acetate.

**3. Ion exchange chromatography:**

*a)* A mixture of amino acids can be separated by ion exchange chromatography. In this method, a mixture of amino acids is applied to a column that contains an insoluble ion exchanger. Under the acidic conditions, all the amino acids have a net positive charge and are bound to the negatively charged ion exchange column. Then each amino acid is sequentially released from the chromatography column by eluting with solutions of increasing ionic strength and pH. As the pH increases, the amino acids lose hydrogen ions, first from -COOH groups and the from $NH_3^+$ and side chains. Thus they become negatively charged and are released from the resin. Each amino acid emerges from the column at a specific pH and ionic strength.




**Determination of the amino acid composition of a polypeptide using an amino acid analyzer**

## II. *Electrophoresis:*

It is the movement of charged particles in an electric field towards the oppositely charged electrode.

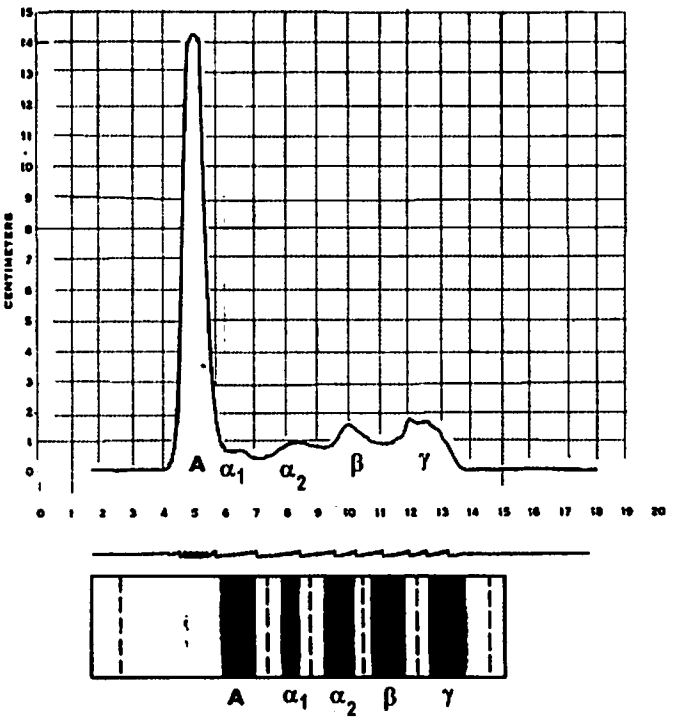
### A. Importance:

By electrophoresis, a mixture of amino acids, polypeptides or proteins can be separated by using electric current.

### B. Procedure:

1. Sample (e.g. serum containing a mixture of proteins) is applied to a strip of filter paper or cellulose acetate. Then both edges of the strip is dipped in alkaline buffer solution.
2. Because proteins are amphoteric, they will carry negative charges in alkaline medium.

3. When the current passes, proteins will migrate towards positive electrode (anode). The rate of migration depends on:
   *a)* The amount of charges carried by each protein.
   *b)* The molecular weight of proteins.
4. By this method, serum proteins can be separated into several bands, each band represents special type of protein. These types are: albumin, globulins[α ($\alpha_1$,$\alpha_2$),β and γ globulins].
5. The density of each band is directly proportional to its serum concentration. So albumin shows the densest band.




**Cellulose acetate electrophoresis pattern of normal human serum. A = Albumin, $\alpha_1$ & $\alpha_2$ = $\alpha_1$ and $\alpha_2$ globulins, β = β globulin and γ = γ globulins.**

## C. Diagnostic importance:

Serum electrophoresis may be used in diagnosis of certain diseases:

1. **Hypoalbuminemia:** (i.e. decreased serum albumin): The albumin band becomes less dense. This occurs for example in advanced **liver disease** as liver is the site of albumin synthesis.
2. **Hypergammaglobulinemia:** (i.e. increased γ-globulins):Occurs in some malignant diseases called: **multiple myeloma.**

## III. *Dialysis:*

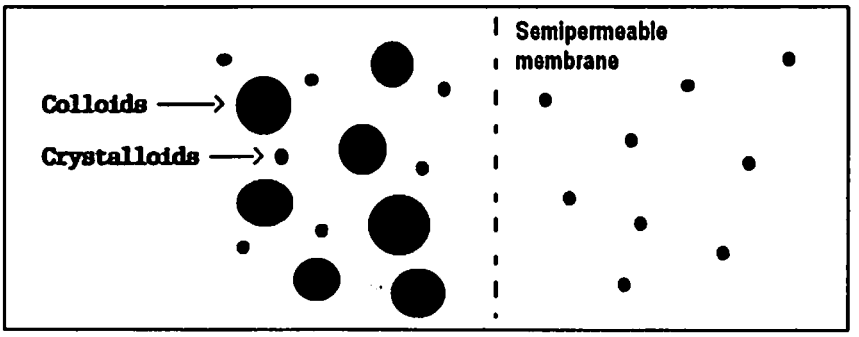
Dialysis means separation of colloids from crystalloids.

A. Proteins have a high molecular weight. They form a colloidal solution.

**B.** If there is a mixture of proteins (colloids) and salts (crystalloids),they can be separated by dialysis i.e. by using a semi-permeable membrane. Crystalloids can pass through this membrane, while colloids cannot due to the large size of their particles.

**C. Medical importance:**

Dialysis is used for renal failure patients. Blood passes through dialyzing machine to get rid of waste products and preserving the plasma proteins.




## IV. *Precipitation:*

Proteins can be separated by different concentrations of salt solutions e.g.

*Albumin is participated by **full** concentration of ammonium sulphate.

*Globulin is participated by **half** concentration of ammonium sulphate.

## V. *Ultracentrifugation:*

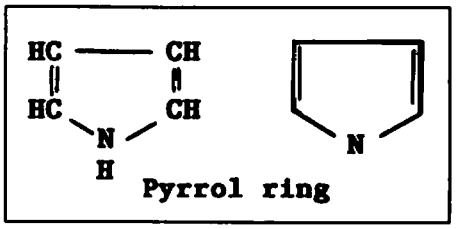
By using a centrifuge of about 40000 rounds per minute (RPM).By this method, a mixture of proteins is separated into different fractions according to their densities.

# *Hemoproteins*

## I. *Definition:*

**A.** Hemoproteins are conjugated protein formed of protein part (globin) and nonprotein prosthetic part (heme).

1. **Heme contains iron** (red in color). Thus hemoproteins are considered metaloproteins.
2. **Hemoproteins include many biologically active compounds as:**
   *a)* Hemoglobin: This carries oxygen.
   *b)* Myoglobin: This stores oxygen in muscles.

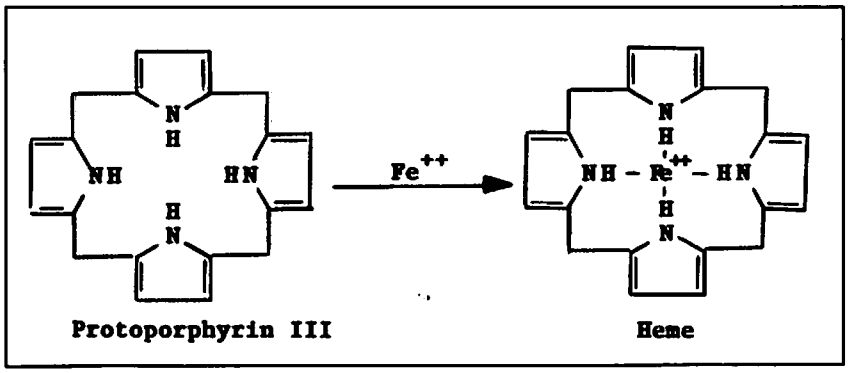


Pyrrol ring

*c)* Respiratory enzymes: These use oxygen.

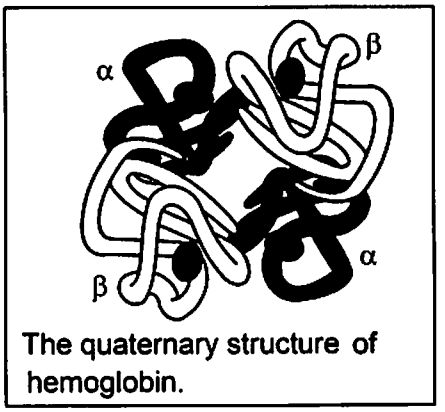
## B. Structure of heme:

1. Four Pyrrol rings are united together to form **protoporphyrin III.**
2. **Iron** in ferrous state ($Fe^{++}$) is incorporated in protoporphyrin III to form heme.




## C. Hemoglobin:

1. It is a metaloprotein formed of heme and globin.
   *a)* Globin is a globular protein rich in histidine amino acids. It forms about 95% of haemoglobin molecule.
   *b)* Globin is a protein having a quaternary structure. It is formed of 2 α chain (each 141 amino acids) and 2 β chains (each 146 amino acids).



The quaternary structure of hemoglobin.

2. **Functions of hemoglobin:**
   *a)* Carries $O_2$ to tissues and removes $CO_2$ from them to the lungs.
   *b)* Acts as blood buffer.
3. Synthesis of heme.
4. Structure of hemoglobin.
5. Properties of hemoglobin.
6. Hemoglobin derivatives.

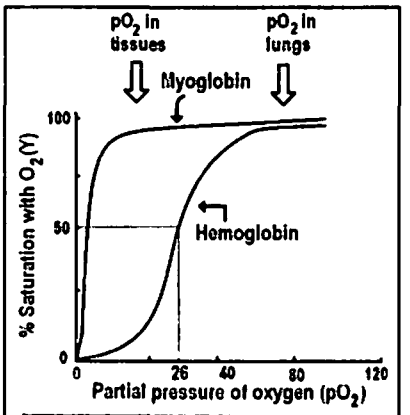
**See chapter of Hb, part III**

## D. Myoglobin:

1. It is found only in the cytosol of **red skeletal** muscles and **cardiac** muscle. It gives these tissues their characteristic red color.
2. It is formed of **one heme molecule** attached to **one polypeptide** chain called **globin.**
3. Myoglobin has much higher affinity for oxygen than hemoglobin. It is unable to release it except under very low oxygen tension.
4. Myoglobin concentration is increased in blood in a disease called **myocardial infraction** (=cardiac muscle disease).

## E. Binding of oxygen to myoglobin and haemoglobin:

1. Myoglobin can bind only one molecule of oxygen because it contains only one heme group. In contrast, hemoglobin can bind one oxygen molecule ($O_2$) at each of its four heme groups. The degree of saturation (Y) of these oxygen binding sites on all myoglobin or haemoglobin molecules can vary between zero (all sites are empty) and 100% (all sites are full).
2. **Oxygen dissociation curve:** A plot of Y measured at different partial pressures of oxygen ($pO_2$) is called the oxygen dissociation curve. The curve for myoglobin and haemoglobin show important differences. The graph beside illustrate that myoglobin has a higher oxygen affinity than does haemoglobin. The partial pressure of oxygen needed to achieve half-saturation of the binding sites ($P_{50}$) is approximately 1 nm Hg for myoglobin and 26 mmHg. [Note: the higher the oxygen affinity (that is, the more tightly oxygen binds), the lower the $P_{50}$].



**Oxygen dissociation curves for myoglobin and hemoglobin.**

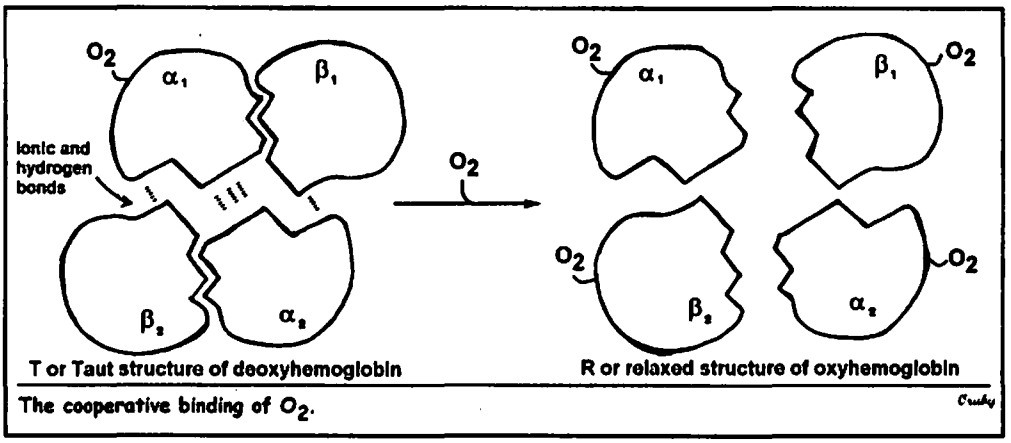
*a)* **Myoglobin:** The oxygen dissociation curve for myoglobin has a hyperbolic shape. This reflects the fact that myoglobin reversibly binds a single molecule of oxygen. Thus, oxygenated ($MbO_2$) and deoxygeneated (Mb) myoglobin exist in a simple equilibrium:

$$Mb + O2 \leftrightharpoons MbO_2$$

The equilibrium is shifted to the right or the left as oxygen is added to or removed from the system.[Note: Myoglobin is designed to bind oxygen released by haemoglobin at the low pO2 found in the muscle. Myoglobin in turn release oxygen within the muscle cell in response to oxygen demand.]

*b)* **Hemoglobin:** The oxygen dissociation curve for haemoglobin is sigmoid in shape, indicating that the subunits cooperate in binding oxygen. This means that the binding of one oxygen molecule at one heme increases the oxygen affinity of the remaining heme groups in the same hemoglobin molecule (the cooperative binding of $O_2$). **Although it is difficult for the first oxygen** molecule to bind to haemoglobin, subsequent binding of oxygen occurs with high affinity as shown by the

steep upward oxygen dissociation curve in the region near 20 to 30 mmHg.




The cooperative binding of $O_2$.

## F. Clinical aspects:

1. **Myoglobinuria:**
   - *a)* It is the release of myoglobin from muscles after massive crush injury.
   - *b)* Myoglobin is excreted in urine, colors it dark. It may cause renal tubular obstruction and renal failure.
2. Plasma myoglobin is increased following **myocardial infarction**, but measurement of serum myocardial enzymes provides a more sensitive index of myocardial infarction.
3. **Sickle cell anemia:**
   - *a)* The red cells of these patients contain abnormal hemoglobin called **hemoglobin S (HbS).**
   - *b)* A molecule of HbS contains 2 normal α-chains and 2 mutant β-chains in which **glutamate** at position six has been replaced by **valine.** (for more details see chapter of haemoglobin, part III).
4. **Thalassemias:** Are anemias characterized by reduced synthesis of either alpha chain (α-thalassemia) or beta chain (β-thalassemia) of hemoglobin.

# Chapter 4 *Chemistry of Nucleoproteins, Nucleotides and Nucleic Acids*

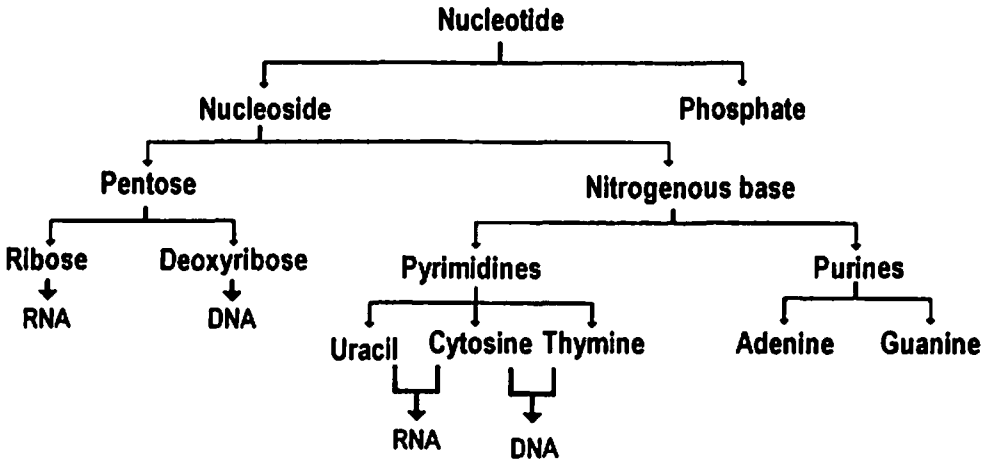
I. ***Nucleoproteins:*** Are conjugated proteins formed of protein part conjugated with nucleic acids (DNA and RNA).

A. **Chromosomes**:

1. These are **nucleoproteins**, formed mainly of DNA and basic proteins (histones). In man they are 46 in number.
2. Functions: Cell division and carry heredity character.

B. **Chromatin**: It is the **chromosomal material** that is formed of a condensed DNA-protein complex.

## II. *Structure of nucleotides:*




A. **Nucleotides**: are intracellular molecules formed of: Base+ Sugar + Phosphate.

| Base | Sugar | Phosphate |
|---|---|---|

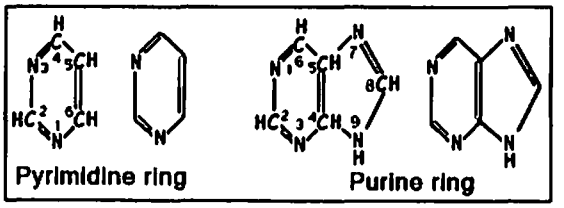
B. **Nucleosides**: are formed only of: nitrogenous bases and sugars.

| Base | Sugar |
|---|---|

C. **Bases**: The nitrogenous bases are either pyrimidines or purines.

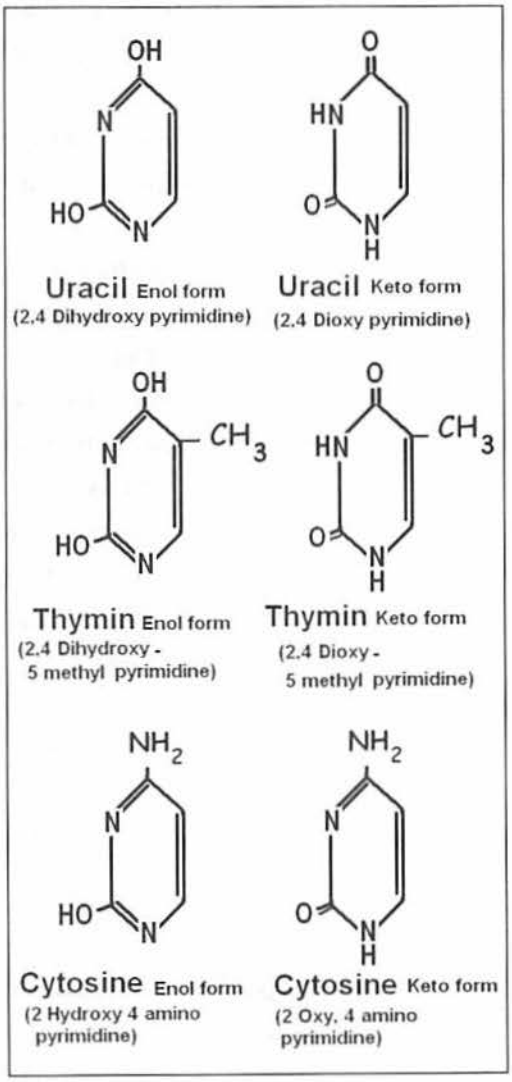
1. **Pyrimidine bases:**

*a)* They contain pyrimidine ring. There are 3 pyrimidines enter in the structure of nucleotides and nucleic acids. These are uracil,



thymin and cytosine. Each one may be present in enol (lactim) form or keto (lactan) form.

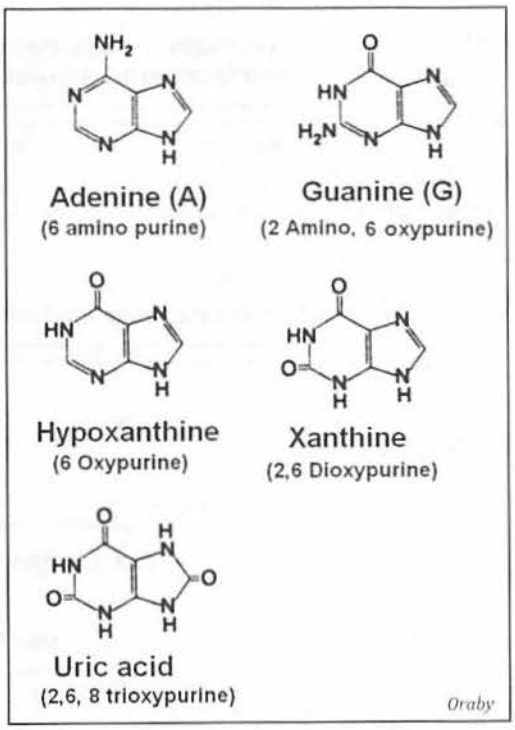
*b)* **Tautomerism:** Purines and pyrimidines are present in two isomeric forms (tautomers): a keto (or lactam) form and enol (or lactim) form. keto form at physiological pH is the predominant of both tautomers.

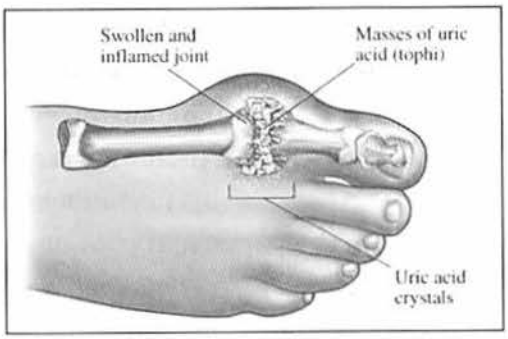



**2. Purine bases:**

*a)* **Adenine and guanine** are the 2 purines which enter in the structure of nucleic acids (DNA and RNA).

*b)* Hypoxanthine, xanthine and uric acid are the end products of adenine and guanine catabolism. Uric acid is excreted in urine. Plasma concentration of uric acid is: 2-7 mg/dl.



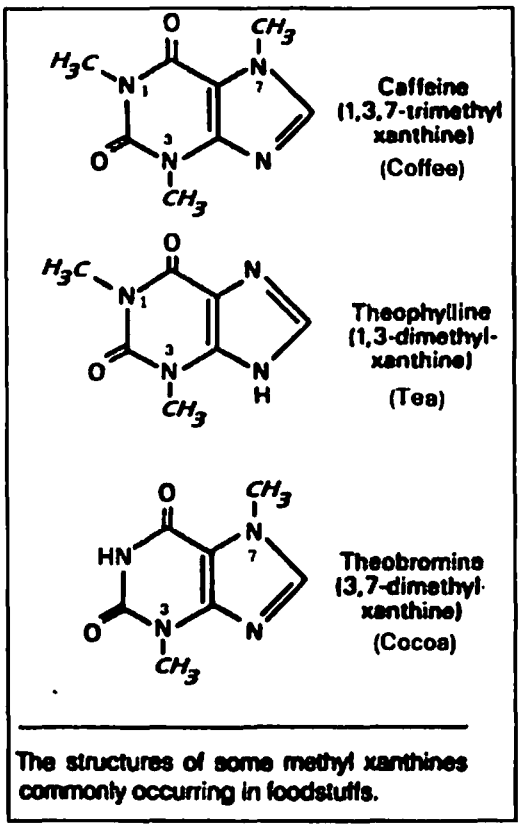

*c)* **Gout:**

Is a disease characterized by an increase of uric acid concentration in plasma. This leads to deposition of uric acid in:

1) **Small joints** especially that of Big toe → swollen, inflamed and severe pain.
2) **Kidney** → kidney stone.
3) **Cartilage** → destruction of cartilage.

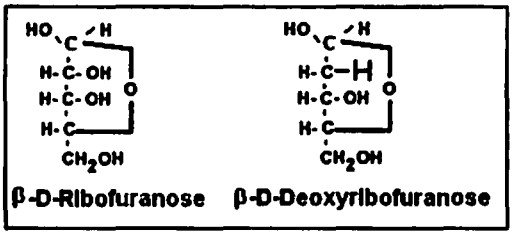
*d)* **Methylated purines (plant xanthines):** Plants contain some natural methylated purines. Many of these have pharmacological action e.g.:

1) **Coffee:** Contains caffeine (1,3,7 trimethylxanthine).
2) **Tea:** Contains thiophylline (1,3 dimethylxanthine).
3) **Cocoa:** Contains thiobromine (3,7 dimethylxanthine).



The structures of some methyl xanthines commonly occurring in foodstuffs.

*e)* **Synthetic bases:** as 5-fluorouracil and 6-mercaptopurine are used as anticancer and antiviral drugs. They compete with natural bases for synthesis of cellular DNA and RNA → inhibition of replication.

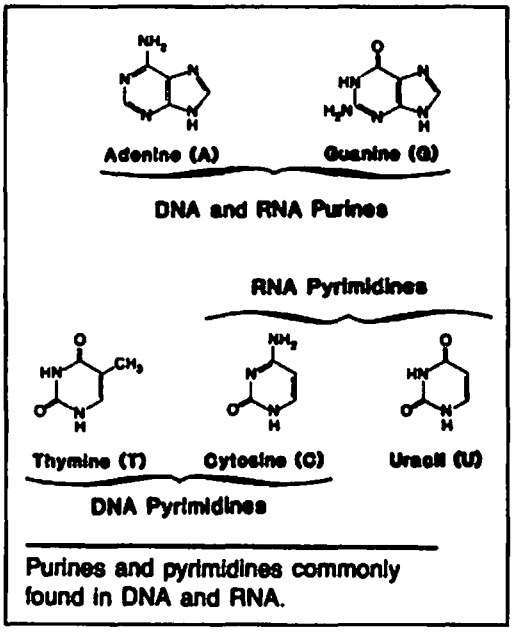



**D. <u>Sugars:</u>** The sugars enter in the structure of nucleotides is either **ribose** (β-D-Ribofuranose) or **<u>deoxyribose</u>** (β-D-deoxyribofuranose).

**1. Site of sugar and phosphate attachment:**

*a)* **Nucleosides:** They are formed by the attachment of $C_1$ of the sugar to the nitrogen 1 of pyrimidine and nitrogen 9 of purine.

*b)* **Nucleotides:** They are formed by the attachment of -OH of phosphate to one of the -OH groups of the sugar molecule.



Purines and pyrimidines commonly found in DNA and RNA.

### E. Nomenclature of different nucleotides and nucleosides:

| Base | Nucleoside (Base + Sugar) | Nucleotide (Base + Sugar + Phosphate) |
|---|---|---|
| **Adenine (A)** | Adenosine | Adenosine monophosphate **(AMP)** |
| | Deoxyadenosine | Deoxyadenosine monophosphate **(d.AMP)** |
| **Guanine (G)** | Guanosine | Guanosine monophosphate **(GMP)** |
| | Deoxyguanosine | Deoxyguanosine monophosphate **(d.GMP)** |
| **Xanthine (X)** | Xanthosine | Xanthosine monophosphate **(XMP)** |
| **Hypoxanthine (I)** | Inosine | Inosine monophosphate **(IMP)** |
| **Cytosine (C)** | Cytidine | Cytidine monophosphate **(CMP)** |
| | Deoxycytidine | Deoxycytidine monophosphate **(d.CMP)** |
| **Uracil (U)** | Uridine | Uridine monophosphate **(UMP)** |
| **Thymine (T)** | Thymidine | Thymjdine monophosphate **(TMP)** |

## III. *Functions of nucleotides:*

A. **They enter in the structure of nucleic acids:** DNA and RNA.

B. **Purines enter in the structure of:**

1. Adenosine triphosphate (ATP). It is a source of energy.
2. Cyclic adenosine monophosphate (cAMP). It is a regulator of carbohydrate and lipid metabolism (see below).
3. Some coenzymes as:
   *a)* Flavin mononucleotide (FMN) and flavin dinucleotide (FAD) (hydrogen carriers).
   *b)* Nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate ($NADP^+$) = (hydrogen carriers).
   *c)* Coenzyme A (CoASH) = Acid carrier.
   *d)* S-adenosyl methionine (methyl donor).

C. **Pyrimidines enter in the structure of:**

1. Uridine diphosphate glucose (UDP-Glucose).
2. Uridine diphosphate galactose (UDP-Galactose).
3. Cytidine diphosphate acylglycerol (CDP-Acylglycerol).

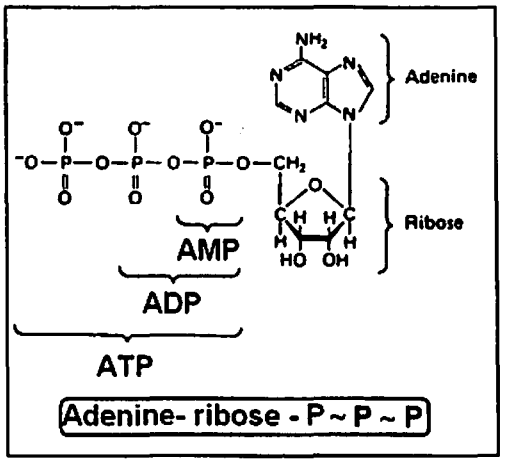
## IV. *Free nucleotides of biological importance:*

### A. Adenosine triphosphate (ATP):

1. **Structure:**
   *a)* ATP is a high energy phosphate compound. It contains 2 high energy bonds (~), between phosphate (1) and (2) and between

phosphate (2) and (3). High energy bond gives upon hydrolysis more than 7000 calories.

*b)* ADP is also high energy compound contains one high energy bond.




**2. Functions of ATP:**

Oxidative reactions of nutrient occur in the body liberate energy. This energy if not stored in the form of ATP will be lost as heat.

***Thus ATP acts as stored form of energy that is used for:***

*a)* Muscle contraction.

*b)* Nerve conduction.

*c)* Absorption and secretion.

*d)* Active transport across cell membranes.

*e)* Activation of some compounds e.g.

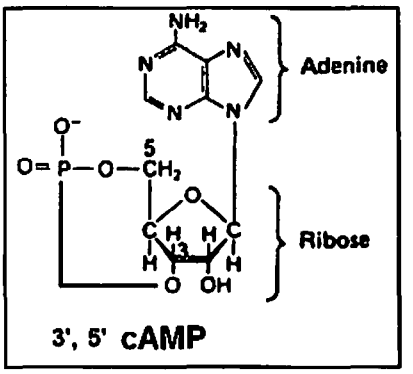
***Glucose + ATP → Glucose-6-phosphate + ADP***

*f)* Synthesis of cyclic AMP and active methionine.

## B. Cyclic AMP (cAMP):

**1. Structure:**

It is similar to AMP but a phosphate group is attached to ribose through 3 and 5 carbons by glycosidic bonds.




**2. Formation:**

It is formed from ATP by adenylate cyclase enzyme and converted to AMP by phosphodiesterase enzyme.


**3. Functions:**

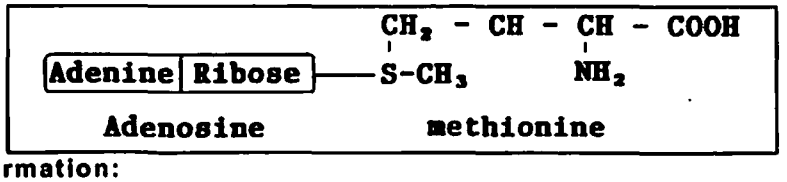
*a)* cAMP acts as **regulator** for carbohydrate and lipid metabolism by activating and inactivating certain enzymes.

*b)* It acts as **second messenger** for some hormones as glucagon, epinephrine and nor epinephrine.

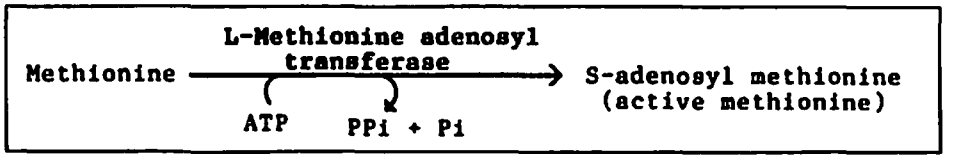
## C. S-Adenosyl methionine (SAM):

**1. Structure:**

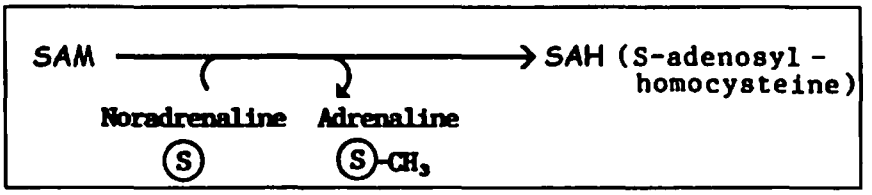
It is active methionine formed of methionine attached to adenosine through $-S-CH_3$ group of the amino acid.




2. **Formation:**

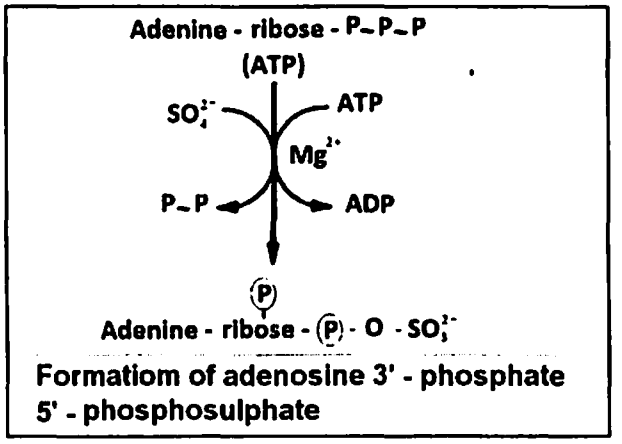



3. **Function:** It is important methyl donor in transmethylation reactions e.g.




## D. Adenosine 3'-phosphate 5'-phosphosulphate, PAPS (active sulfate):

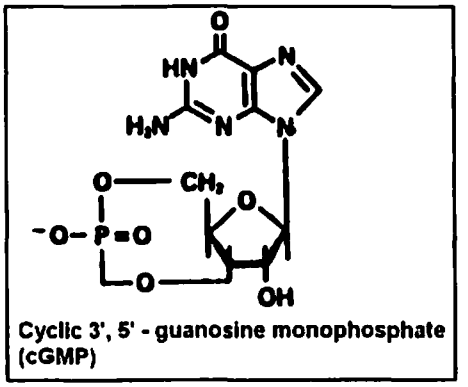
1. **Functions:**
   - *a)* It acts as **sulfate donor** for the formation of sulfated proteoglycans.
   - *b)* It acts as sulfate donor for metabolites of some drugs which are excreted in urine as sulfate conjugates.




Formatiom of adenosine 3' - phosphate 5' - phosphosulphate

## E. Guanosine derivatives (guanosine mono [GMP], di [GDP] and triphosphate [GTP]):

1. GTP is used as a source of energy.
2. Cyclic GMP (cGMP) acts as a second messenger for some hormones.




Cyclic 3', 5' - guanosine monophosphate (cGMP)

## F. Cytidine derivatives (Cytidine mono [CMP], di [CDP] and tri-phosphate [CTP]):

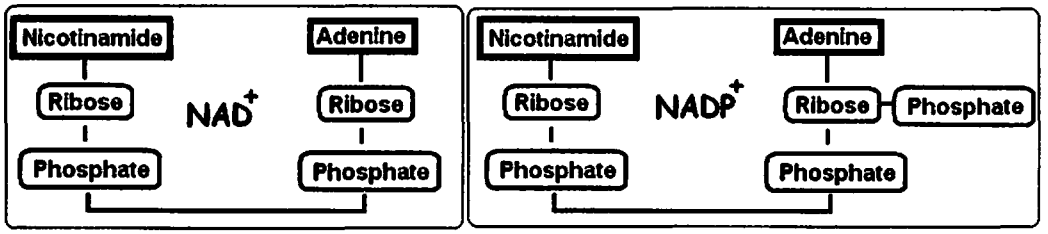
1. CTP is required for biosynthesis of some phospholipids.

G. **Uridine derivatives** (Uridine mono [UMP],di [UDP] and triphosphate [UTP]):

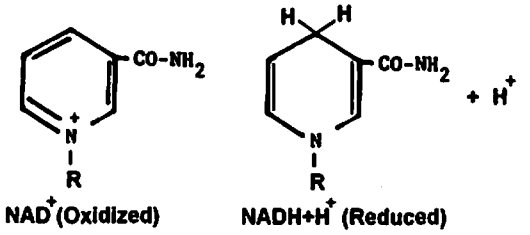
1. **UDP-Glucose** UDP-galactose is used in synthesis of lactose, glycogen and glycolipids.
2. UDP-Glucuronic acid is used for:
   *a)* **Synthesis of Glycosaminoglycans (GAGs).**
   *b)* **Conjugation reactions** (e.g. conjugation with bilirubin).
3. UDP-Glucosamine, UDP N-acetylglucosamine and UDP-N-acetyl-galactosamine are used in the synthesis of many compounds in the body e.g. glycoproteins, glycolipids and GAGs.

H. **Coenzymes nucleotides in nature**: All are vitamin B complex derivatives: **These are $NAD^+$, NADP, FAD, FMN and coenzyme A.**

1. **NAD (Nicotinamide adenine dinucleotide):**
   *a)* It is called dinucleotide because it contains 2 nucleotides:
      1) Nicotinamide-Ribose-phosphate.
      2) Adenine-Ribose-phosphate.
   *b)* Nicotinamide is nicotinic acid (niacin) derivative. Niacin is a member of vitamin B-complex.
   *c)* $NADP^+$ is similar in structure of $NAD^+$ except it contains a third phosphate group attached to $C_3$ of adenine nucleotide (*).
   *d)* Both $NAD^+$ and $NADP^+$ are coenzymes and act as hydrogen carriers. $NAD^+$ ($NADP^+$) + 2H ⇆ NADH+$H^+$ (NADPH+$H^+$)




   *e)* Nicotinamide is present in 2 forms: oxidized and reduced.

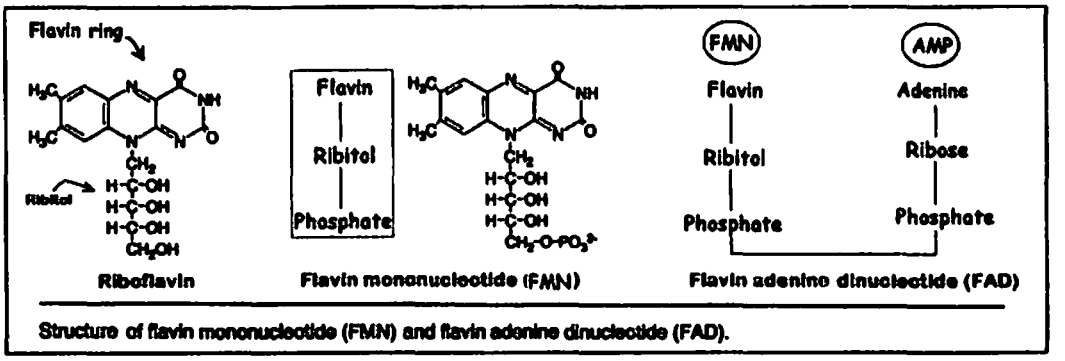



2. **FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide):**
   *a)* FAD is called dinucleotide because it contains 2 nucleotides:
      1) Flavin-ribitol-phosphate (FMN).

2) Adenine-ribose-phosphate (AMP).

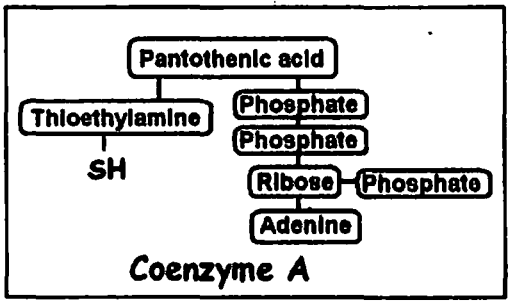
*b)* FMN is composed only of flavin, ribitol and phosphate.

*c)* FAD and FMN are coenzymes and act as **hydrogen carriers.**




Structure of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD).

**3. Coenzyme A:**




*a)* Coenzyme A is composed of Pantothenic acid, thioethylamine, 2 molecules of phosphate, phosphoribose and adenine.

*b)* Functions: It acts as acid carrier e.g. acetic acid, succinic acid, fatty acids and other carboxylic acids e.g. acetyl CoA.

# *Nucleic acids*

Nucleic acids are polynucleotides. They are 2 types: DNA and RNA.

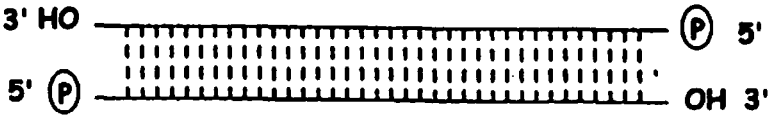
## I. *Deoxyribonucleic acid (DNA):*

### A. Site:

1. Human DNA is present in nucleus and mitochondria.

### B. Structure:

1. Human DNA consists of 2 strands (chains) of polynucleotides. Each nucleotide is composed of base, sugar and phosphate.

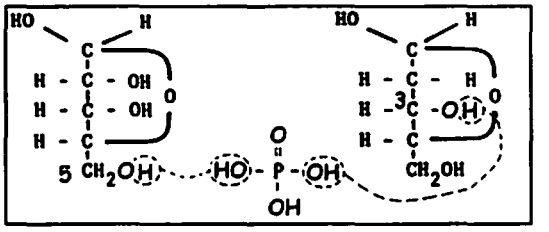



*a)* **The number of nucleotides in DNA** may reach millions.

*b)* **The bases** in DNA are: guanine, adenine, cytosine and thymine.

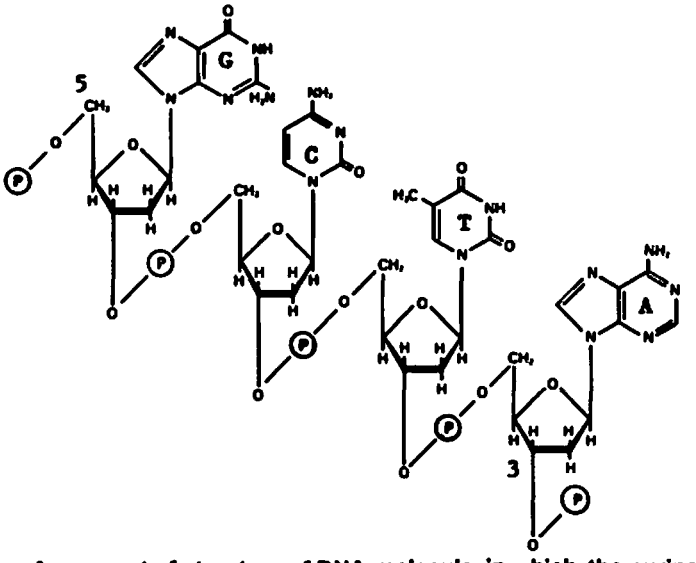
*c)* **The sugar** is deoxyribose. So, the nucleotides are named: **d-GMP, d-AMP, d-CMP and d-TMP.**

*d)* The nucleotides are arranged in chains linked together by **phosphodiester bond** between $C_5$ of deoxyribose of one nucleotide and $C_3$ of the next one.



**Note:** Phosphodiester bond means one phosphate is linked to 2 sugars → 2 ester bonds.

Each polynucleotide chain has **2 terminals**. At one terminal, phosphate is only attached to $C_5$ of first pentose. At the other one, phosphate is only attached to $C_3$ of last pentose. The nucleotides in the polynucleotide chain are always read in the 5' - 3' direction.



**A segment of structure of DNA molecule in which the purine and pyrimidin bases; (A), (G), (T) and (C) are held together by phosphodiester backbone.**

**2. Assembly of double strands of DNA:**

*a)* The link between 2 strands is through the bases.

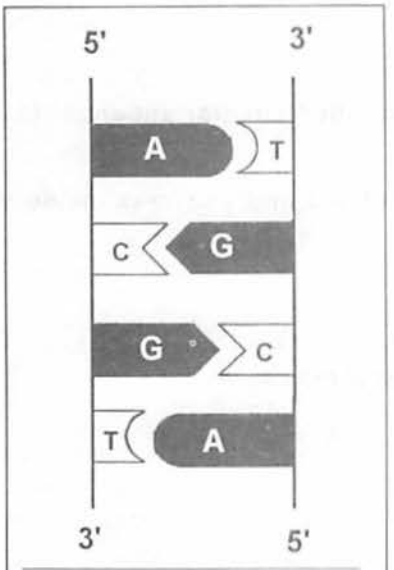
*b)* **Pairing role**: in DNA molecule:

1) Adenine is paired only with thymine (A=T) by 2 hydrogen bonds.

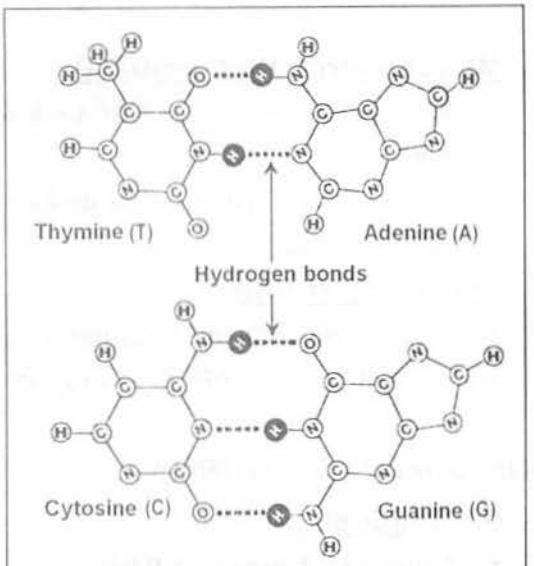
2) Guanine is paired only with cytosine (G≡C) by 3 hydrogen bonds.

i- Thus in double stranded DNA molecule, the content of adenine equals that of thymine and the content of guanine equals that of cytosine.

ii- Also the G ≡ C bond (3 hydrogen bonds) is stronger by about 50% than A = T (2 hydrogen bonds).




Two complementary DNA sequences.

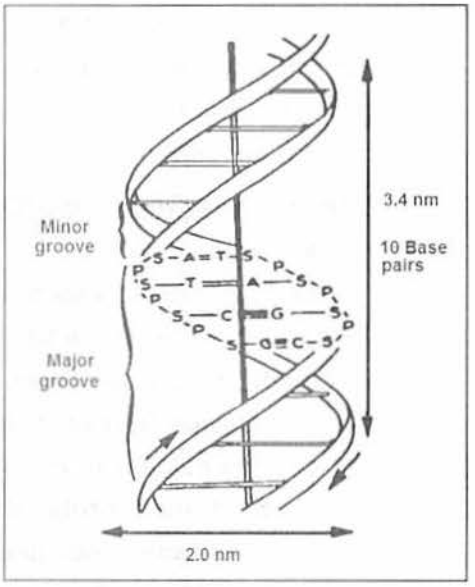



Hydrogen bonds between complementary bases.

*c)* **Helical structure of DNA:**

DNA molecules run in the form of double helix.

1) **The helical structure of DNA** is present at least in 6 forms: A, B, C, D, E and Z. The B form is usually found under physiologic conditions.
2) A single turn of B form of DNA around the axis of the molecule contains **10 base pairs.**
3) The distance between one turn and the next is about **3.4 nm.**
4) The width (helical diameter) of double helix in B form is **2 nm.**
5) Two grooves are present in double helix DNA, **major groove** (2.2 nm) and **minor groove** (1.2 nm).Through these grooves many drugs and proteins can make contact with nitrogenous bases without need to open the helix.
6) **Comparison of different forms of DNA:**




| | Z-Form | B-Form | A-Form |
|---|---|---|---|
| One turn span | 3.8 nm (Longer) | 3.4 nm (Medium) | 2.3 nm (Shorter) |
| Diameter | 1.8 nm (smaller) | 2 nm (Medium) | 2.6 nm (Larger) |
| Direction of the double helix | Left | Right | Right |
| Number of bP/ turn | 12 | 10.4 | 11 |

### C. Mitochondrial DNA (mtDNA):

1. It is present in the form of double stranded circular supercoil (2-10 copies).
2. It directs the synthesis of certain proteins and enzymes inside the mitochondria.

### D. Functions of DNA:

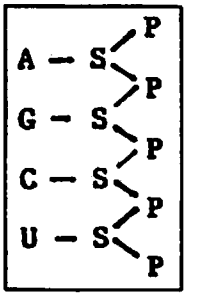
1. Replication of DNA (= reproduction).
2. Transcription of mRNA (= protein biosynthesis).

## II. *Ribonucleic acids (RNA):*

### A. Introduction:

1. **There are 3 types of RNA:**
   - *a)* Messenger RNA = mRNA.
   - *b)* Transfer RNA = tRNA.
   - *c)* Ribosomal RNA = rRNA.
2. All RNA molecules are formed in the nucleus under the control of DNA and the enzyme RNA polymerase.
3. All are formed of one strand only.

### B. Messenger RNA = mRNA:

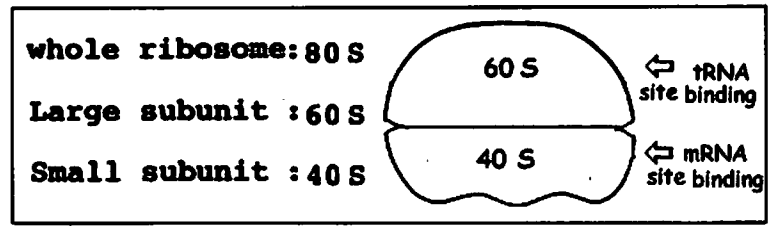



1. **Structure**
   - *a)* It is one stranded nucleic acid, and form about 5% of cellular RNA.
   - *b)* It is formed under the control of DNA in the nucleus (transcription).
   - *c)* It is composed of 400-4000 nucleotides.
   - *d)* **Each nucleotide is formed of base + sugar + phosphate:**
     1) **Bases:** Adenine, guanine, cytosine and uracil.
     2) **Sugar:** Ribose.
     3) **Phosphate.**
2. **Function:**
   - *a)* mRNA carries the genetic information from DNA in the nucleus to the ribosome where protein biosynthesis occurs.
   - *b)* The sequence of nucleotides in the mRNA determines the sequence of amino acids in protein structure.

> ***DNA sequence → mRNA sequence → amino acid sequence in protein (= genetic information = central dogma).***

## C. Ribosomal RNA (rRNA):

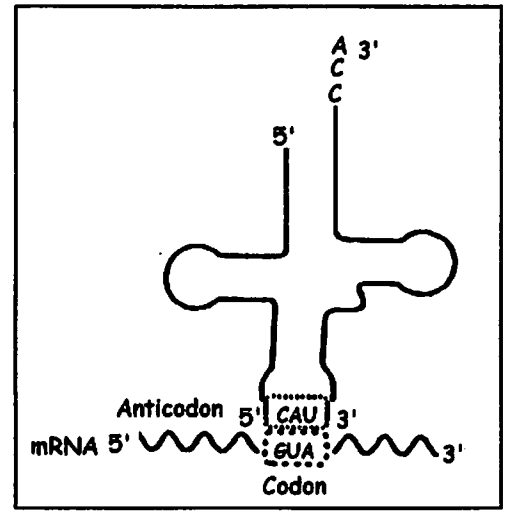
1. It is the nucleic acid present in ribosomes where protein biosynthesis occurs.
2. It forms 80% of the total amount of cellular RNA.
3. It is formed in the nucleus under the control of DNA as a large precursor molecule.
4. In the nucleus, this precursor is divided into 2 subunits: one about twice the size of the other. Then the 2 subunits pass to the ribosomes.
5. The whole ribosome and each subunit has its own sedimentation rate. This rate is measured by what is called: **Svedberg units = S.**




6. The large subunit (60 S) is the binding site for tRNA, while the small subunit (40 S) is the binding site for mRNA.

## D. Transfer RNA (tRNA):

1. tRNA transport amino acids to the ribosome for synthesis of protein. They form 15% of the cellular RNA.
2. Each tRNA has an average length of 75 nucleotides and each one binds to a specific type of amino acid. There are at least one type of tRNA for each of the 20 amino acids that are commonly found in proteins.
3. Due to the interactions of bP, it is coiled and form four main loop (bP in RNA is formed of A to U & G to C).

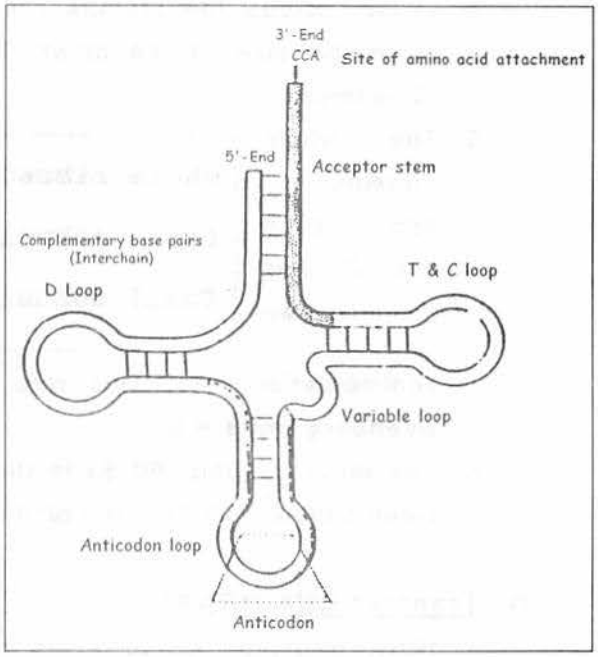



4. **The acceptor arm of tRNA** terminates at its 3' OH end by a specific sequence formed of CCA. Amino acids are carried in the form of aminoacyl group connected to the 3'-hydroxyl group of the acceptor arm. The unpaired loops of tRNA are named according to their unique structures.
   *a)* **Loop I** varies in size from 7 to 11 unpaired bases and it contains the unusual base dihydrouracil so termed the D-loop.

*b)* **Loop II** contains the three specific bases known as the anticodon loop. This portion of tRNA plays a key role in translation by pairing with the complementary codon of mRNA and helps in placing each amino acid in its proper site in the polypeptide chains of proteins.

*c)* **Loop III** contains from 3 to 12 bases and it is the major site for variation in tRNA, so termed the variable loop.

*d)* **Loop IV** contains the unusual thymine and pseudouridine bases, so termed the T & C loop.




**5. Function of tRNA:**

tRNA acts as a carrier for amino acids from the cytoplasm to ribosomes where protein biosynthesis occurs. Each amino acid has one or more specific tRNA.

## III. *Differences between DNA and RNA:*

| | DNA | RNA |
|---|---|---|
| **Site** | • Nucleus<br>• Mitochondria | Cytosol |
| **Functions** | • Carries genetic information.<br>• (cell division) Replication of DNA<br>• Synthesis of mRNAs (Transcription). | Protein synthesis |
| **Structure** | Polynucleotides contain:<br>• Bases: Adenine, guanine, cytosine and **thymine**<br>• Sugar: Deoxyribose. | Polynucleotides contain:<br>• Bases: Adenine, guanine cytosine and **uracil**.<br>• Sugar: Ribose. |
| **Types** | One type | 3 types:<br>• Messenger RNA<br>• Transfer RNA<br>• Ribosomal RNA |
| **No. of strands** | 2 strands in the form of double helix | One strand only |

## IV. *Composition of viral and bacterial nucleic acids:*

### A. Viral nucleic acids:

1. Viruses are composed of nucleic acids enclosed in a protective protein coat **(capsid).**
2. The nucleic acid may be a single or double stranded DNA (ss DNA or ds DNA) or single or double stranded RNA (ss RNA or ds RNA).

### B. Bacterial DNA:

It is present in the form of double stranded circular DNA.

# Chapter 5 *Enzymes*

I. ***Introduction:*** Enzymes are energy barriers separating the reactants (substrates) and the products.

$$\text{Substrates} \xrightarrow{\text{Enzyme}} \text{Products}$$

Note: (en = in, zyme = yeast).

## II. *Definitions:*

A. **Enzymes:** These are specific protein catalysts that:

1. Accelerate the rate of chemical reactions.
2. Enzyme structure is not changed by entering the reactions,
3. Enzyme does not affect the equilibrium constant (i.e. end products) of the reactions.

> **Note: Catalysts:** are substances that accelerate the rate of chemical reactions. They may be organic and inorganic:
>
> 4. **The organic catalysts are enzymes that:**
>    *a)* Highly specific i.e. catalyze one or two reactions only.
>    *b)* Protein in nature, so they are denaturated by heat.
> 5. **The inorganic catalysts are metals:** as zinc, magnesium and chloride ions that:
>    *a)* Non specific i.e. catalyze many reactions.
>    *b)* Not affected by heat.

B. **Rate of chemical reaction:** It is the change in the amount (moles, grams) of starting materials (substrates) or products per unit time.

C. **Substrate:** Is the substance upon which the enzyme acts.

## III. *Cellular distribution of enzymes:*

A. **Intracellular enzymes:** Produced and act inside the cells e.g. metabolic enzymes.

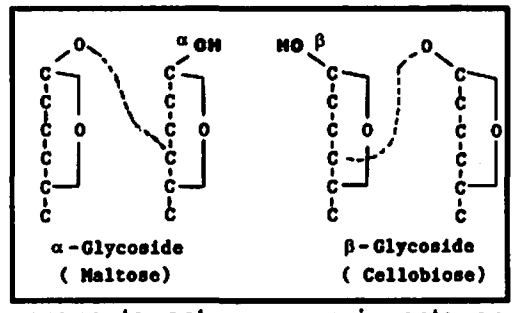
B. **Extracellular enzymes:** Produced inside the cells and act outside the cells e.g. digestive enzymes.

## IV. *General characteristics of enzymes:*

### A. Properties of enzymes:

1. They are protein in nature.
2. They act within a moderate pH and temperature range.
3. They are highly specific, catalyzing only one type of chemical reaction. There are 6 types of specificity.

### B. Enzyme specificity:




1. **Optical (stereo) specificity:** Enzymes act on one of 2 isomers e.g. maltase acts on α -glycosides and not β-glycosides.
2. **Group specificity:** Enzymes need the presence of certain group to act e.g. pepsin acts on peptide bonds.
3. **Absolute specificity:** One enzyme acts only on one substrate e.g. urease enzyme acts only on urea.
4. **Relative specificity:** One enzyme acts on a group of compounds having the same type of bonds e.g. lipase enzymes act on different triacylglycerols.
5. **Reaction specificity:** There are six enzyme classes (see later). Each class has its own specific substrates.
6. **Dual specificity:** One enzyme acts on 2 different substrates e.g. isocitrate dehydrogenase enzyme acts on isocitrate and oxalosuccinate.

### C. Genetic expression of enzymes:

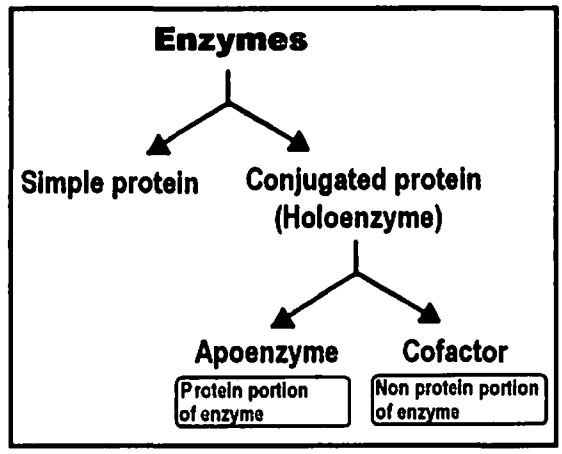
1. Living cells contain a unique set of enzymes, which determine the function of the cell.
2. The set of enzymes in each cell is genetically determined.
3. Genetic disorders may lead to various diseases.

## V. *Enzyme structure and activity:*

### A. *Structure of enzyme:*

1. Enzymes are either simple or conjugated proteins.
2. If the enzyme is a simple protein, only the native conformation of the protein is required for activity.
3. If the enzyme is a conjugated protein, it is called: **holoenzyme** and its activity will depend upon:
   *a)* Conformation of the protein which is called **apoenzyme.**
   *b)* The availability of a non protein part which is called **cofactor.**

1) Cofactors may be metals as $Mg^{2+}$ or $Cu^{2+}$, or **coenzymes** as $NAD^+$, and FAD.
2) In some enzyme systems, the coenzyme is tightly bound to the enzyme protein as in case of FAD. In such cases, the cofactor is called a **prosthetic group.**

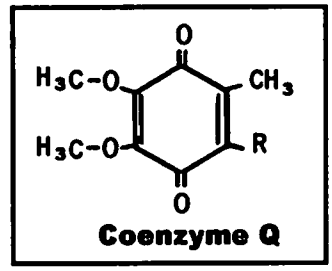



***Differences between apoenzyme and cofactor:***

| *Apoenzyme* | *Cofactor* |
|---|---|
| 1. Protein in nature. | Non protein. |
| 2. Heat labile. | Heat stable. |
| 3. High molecular weight. | Low molecular weight. |
| 4. Non dialyzable. | Dialyzable |

B. ***<u>The important coenzymes are:</u>***

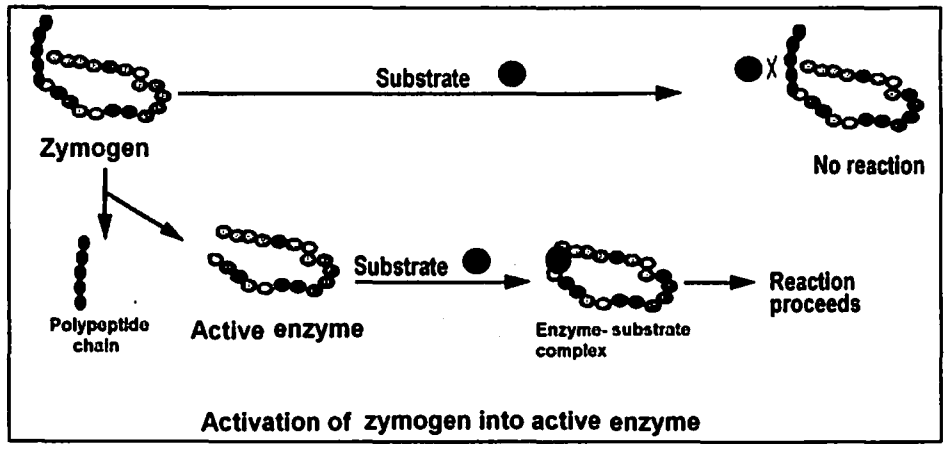
1- **Hydrogen carriers:**
   a) $NAD^+$ and $NADP^+$.
   b) $FAD^+$ and $FMN^+$.
   c) Lipoic acid.
   d) Coenzyme Q.




2- **Carriers of groups other than hydrogen:**
Most of them are derived from vitamins (see chapter of vitamins, part I):
   *a)* Coenzyme A = acid carrier.
   *b)* Thiamine diphosphate (TPP): $CO_2$ and ketol group carrier.
   *c)* Biotin = $CO_2$ carrier.
   *d)* Pyridoxal phosphate = amino ($-NH_2$) group carrier.
   *e)* Folic acid = one carbon group carrier.
   *f)* Cobalamine = methyl group carrier.

C. ***<u>Zymogens:</u>*** They are inactive enzymes.

1. Zymogens are inactive because their catalytic sites are masked by a polypeptide chain.
2. Activatation of zymogen, into active enzyme is done by **removal** of the polypeptide chain to open the catalytic site for its substrate.
3. **Examples** of zymogens: are pepsinogen and trypsinogen.




Activation of zymogen into active enzyme

D. ***Measures of enzyme activity:***

1. **Katal:** (kat) is the amount of enzyme activity that transforms 1 mol of substrate per second.
2. **Unit of enzyme activity:** is the amount of enzyme causing transformation of one micromole (1 µmol) of a substrate per minute at 25 °C under optimal conditions of measurement.
3. **Specific activity:** is the number of units of enzyme activity per milligram of enzyme protein.

**VI.*Enzymes nomenclature (naming):*** There are several ways of naming enzymes:

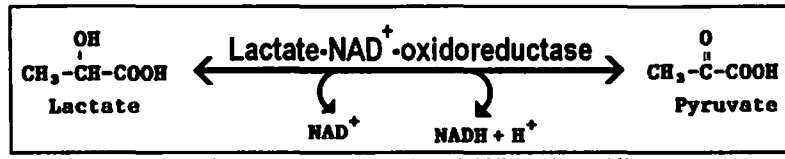
A. Some enzymes were named by attaching the **suffix -ase** to the name of the substrates e.g. maltose and maltase.

B. Some enzymes were named according to the type of the reaction e.g. aminotransferase that transfer amino group..

C. To standardize enzyme nomenclature, the **International Union of Biochemistry (IUB)** made a systemic name to each enzyme. This name can indicate:

1. The substrate acted upon.
2. The coenzyme involved in the reaction.
3. The type of reaction catalyzed.

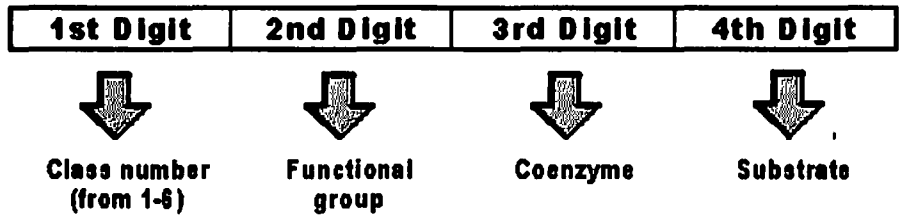
e.g. ***Lactate - NAD$^+$ - oxidoreductase enzyme.*** (Its old name was lactate dehydrogenase). It catalyzes the following reaction:




D. In addition to naming enzymes, the (IUB) classifies enzymes by giving each enzyme a number. This number is called: **Enzyme commission numerical code (EC)** and it contains 4 digits:

1. **First digit:** indicates the class of the enzyme. There are 6 classes of enzymes.

2. **Second digit:** indicates the functional group upon which the enzyme acts e.g. -OH,-CHO……..
3. **Third digit:** indicates the coenzyme e.g. NAD, FAD.
4. **Fourth digit:** indicates the substrate of the enzyme.




e.g. Alcohol-$NAD^+$- dehydrogenase: E.c. 1.1.1.1

$$R\text{-}CH_2\text{-}OH + NAD^+ \rightarrow R\text{-}CHO + NADH + H^+$$

E.C (1): Class of enzyme:oxidoreductase.

E.C.1.(1): Group upon which the enzyme acts is : **CH-OH.**

E.C.1.1.(1):The coenzyme is $NAD^+$.

E.C.1.1.1.(1):Alcohol e.g. ethanol is the substrate.

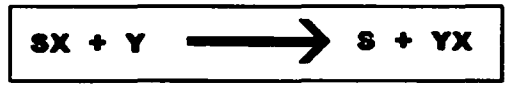
**VII.** ***Classification of enzymes:*** There are 6 classes of enzymes which are:

A. **Oxidoreductases:** This group of enzymes catalyzes an oxidation-reduction reaction between two substrates:

**S (oxidized) + *Y (reduced)* → S *(reduced)* + *Y* (oxidized).**

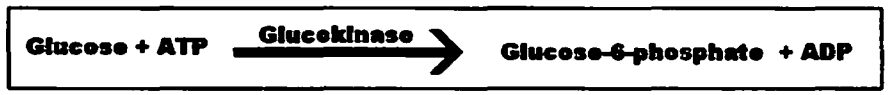
1. Oxidoreductases are further classified according to the substrate oxidized and to the mechanism of oxidation.
2. The mechanism of oxidation is either by removal of hydrogen **(dehydrogenases)** or by addition of oxygen **(oxidases).**
3. Example of oxidoreductases includes the respiratory chain enzymes (see biological oxidation).

B. **Transferases:** This group of enzymes catalyzes the transfer of a group other than hydrogen from one substrate to another:




1. They are further classified according to the group transferred into: phosphotransferases, transaminases, transketolases, trans-acylases, transformylases and transmethylases. Synthase enzymes are transferase enzymes.
2. **Example:**

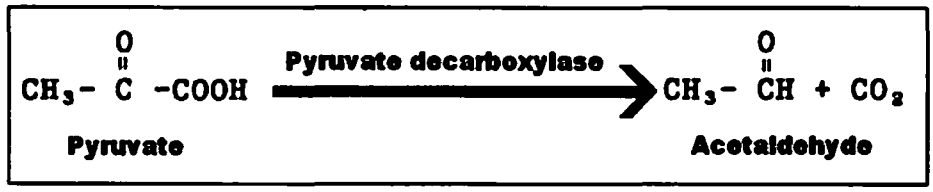
*a)* Phosphotransferases: Kinases:



*b)* Acyltransferases: synthases:

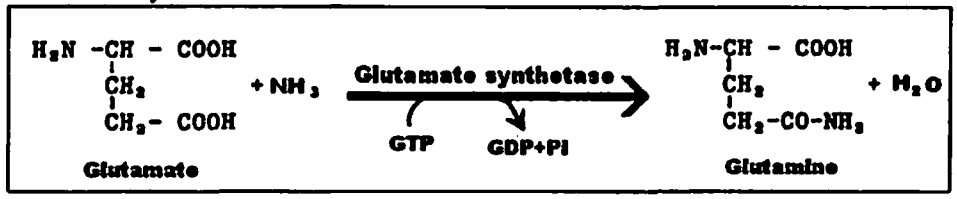

C. **Hydrolases:** this group catalyzes hydrolysis i.e. breakdown of a chemical bond by addition of water: A-B $\xrightarrow{HOH}$ AH + BOH
**Example:** peptidase:


D. **Lyases:** This group of enzymes catalyzes addition of carbon dioxide, water and ammonia across double bonds, or remove these elements to produce double bonds. **Example:** Decarboxylase:




E. **Isomerases:** This group of enzymes catalyzes the interconversion of one isomer into another. This group includes: Isomerases, mutases and epimerases. **Example:** phosphohexose isomerase:


F. **Ligases (or synthetases):** This group of enzymes catalyzes joining of two substrates using the energy from ATP or GTP. **Example:** Glutamine synthetase.



**Summary of enzyme classes:**

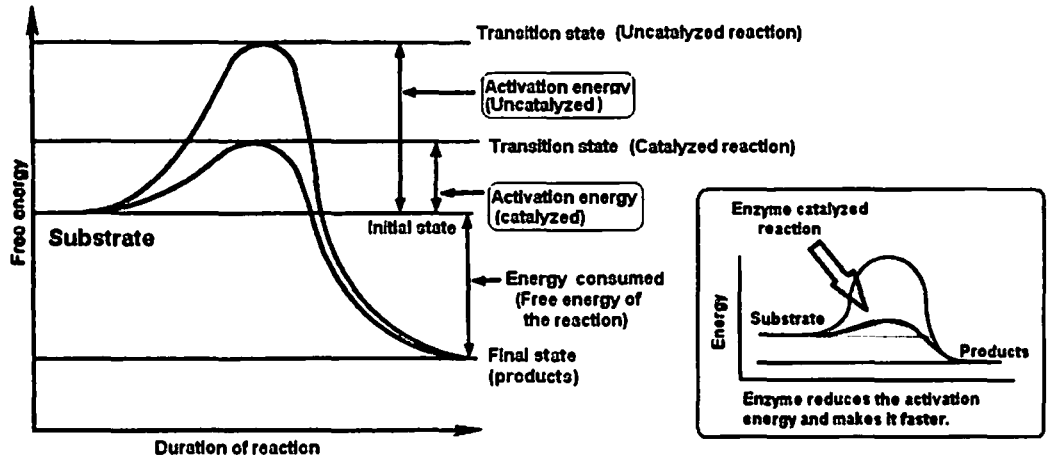
| Number | Classification | Catalytic activity |
|---|---|---|
| 1. | Oxidoreductases | They catalyze an oxidation-reduction reaction between two substrates. |
| 2. | Transferases | They catalyze the transfer of a functional group other than hydrogen from one substrate to another. |
| 3. | Hydrolases | They catalyze hydrolysis i.e. breakdown of a chemical bond by addition of water. |
| 4. | Lyases | Add water, ammonia or carbon dioxide across double bonds, or remove these elements to produce double bonds. |
| 5. | Isomerases | They catalyze the interconversion of one isomer into the other. |
| 6. | Ligases | Catalyze reactions in which two chemical groups are joined (or ligated) with the use of energy from ATP. |

## VIII. *Mechanism of enzyme action:*

### A. Activation Energy:

1. All the reactions that proceed from initial substrates (initial state) to products (final state) consume energy. This is called free energy of the reaction.
2. However the substrates do not become products directly, but must be energized (absorb energy) to reach an activated or transition state. This energy is called activation energy.
3. At transition state, there is a high probability that a chemical bond will be made or broken to form the product.

4. **The definition of activation energy:** is the amount of energy required to raise all the molecules in one mole of a substance to the transition state.
5. **The effect of enzymes:** is to decrease the energy of activation.




**Activation energy**

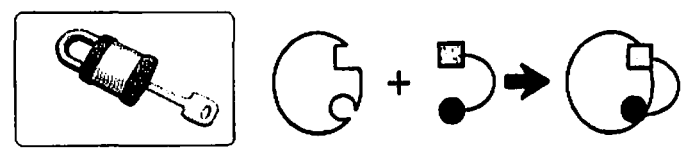
## B. Active site:

1. The specificity of an enzyme is determined by:
   *a)* The functional group of the substrate (or product).
   *b)* The functional group of the enzyme and its cofactors.
   *c)* The physical proximity of these various functional groups:
      1) During the enzyme action, there is a temporary combination between the enzyme and its substrate forming enzyme-substrate complex. This occurs at active site of enzyme.
      2) This is followed by dissociation of this complex into enzyme again and products.


## C. Theories of enzyme action:

Two theories have been proposed to explain the specificity of enzyme action:

*a)* **The lock and key theory:** The active site of the enzyme is complementary in conformation to the substrate, so that enzyme and substrate "recognise" one another.



Lock and key theory

*b)* **The induced fit theory:** The enzyme changes shape upon binding the substrate, so that the conformation of substrate and enzyme protein are only complementary **after** the binding reaction.

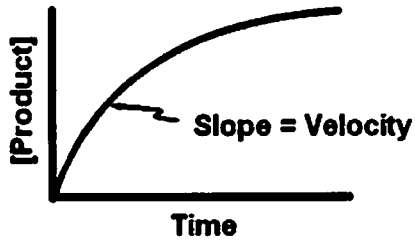

**Induced fit theory**

**IX.*Enzyme kinetics:*** It is the study of the velocity (rate) of reactions catalyzed by enzymes.

**A. Velocity of reaction:** It is the increase in the concentration of product (or decrease in concentration of substrate) with time.

**B. Initial velocity:**

1. If an enzyme is incubated with its substrate and the appearance of the product with time is recorded on a graph, the resulting line will have the hyperbolic shape as in the figure:

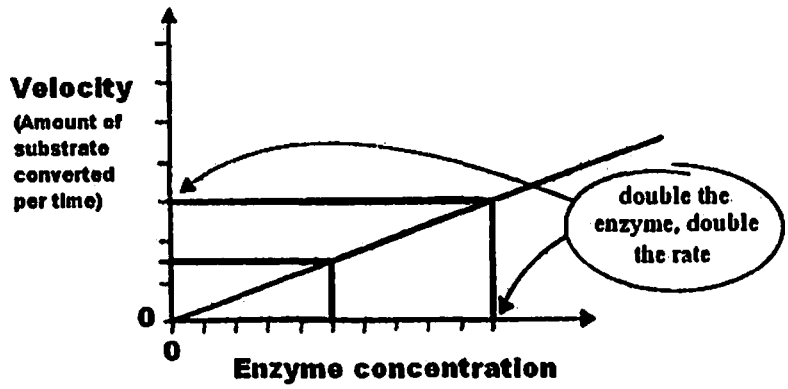



2. The rate (velocity) of the reaction, which corresponds to the slope of this curve, is initially constant but gradually decreases.
3. **The decline in the rate of the reaction may be due to:**
   *a)* Depletion of the substrate,
   *b)* Inhibition of the enzyme by its product.
   *c)* Denaturation of the enzyme.
4. ***Initial velocity (Vi) of the reaction:*** **It is the initial portion of the reaction where the increase in the concentration of the product is correlated constantly with time.**
   For this reason, only the initial velocity (Vi) is used in calculating the kinetic parameters of the reaction.
5. **The units of velocity**: are concentration of the product per unit time, e.g. micromoles / minute.

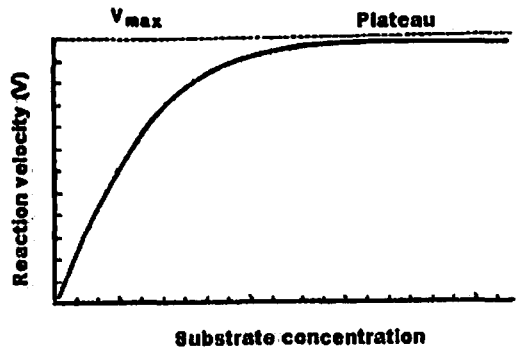
## C. *Factors affecting enzyme activity:*

**Factors affecting enzyme activity:**
- **Enzyme concentration**
- **Substrate concentration**
- **pH**
- **Temperature**
- **Enzyme activators**
- **Enzyme inhibitors**

1. **Concentration of enzyme:** The initial velocity of a reaction is directly proportional to the amount of the enzyme present, provided that all other conditions remain constant. *(Note: when the amount of enzyme in a reaction is doubled, the amount of substrate converted to product is doubled. Also when the amount of enzyme is tripled, the amount of substrate converted to product is tripled and so on).*



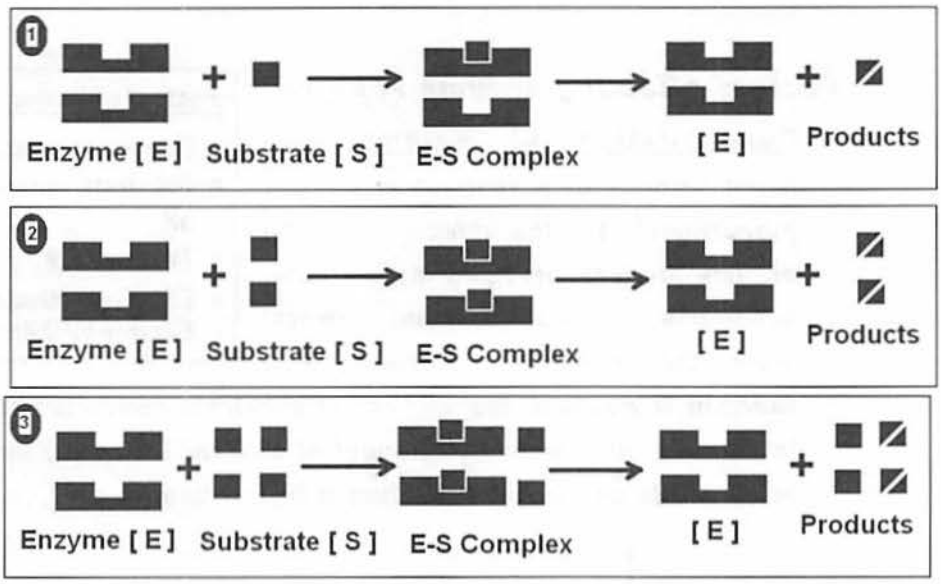

2. **Concentration of substrate:** The initial velocity of a reaction is directly proportional to the amount of substrate present till it reaches a maximum point known as **maximum velocity ($V_{max}$)**, where any further increase in the amount of substrate causes no increase in the velocity of the reaction. This is true if all other conditions especially enzyme concentration remain constant.




**Important notes about concentration of substrate:**

*a)* **Explanation of effect of substrate concentration:**

1) At low substrate concentration, not all enzymes are saturated. So the rate of reaction will increase.
2) At higher substrate concentration, all enzymes get saturated with substrates and any more increase of substrate concentration will result in no increase in the rate of the reaction (plateau curve).This can be explained by the following diagram:




*b)* **Michaelis-Menten Equation:**

1) This equation describes the dependence of reaction velocity on substrate concentration.
2) Michaelis and Menten proposed that in any enzymatic reaction, the enzyme (E) combines with substrate (S) to form an enzyme-substrate (ES) complex.
3) ES then breaks down either to enzyme and substrate again or to enzyme and product (P).

$$E + S \underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}} ES \xrightarrow{K_2} E + P$$

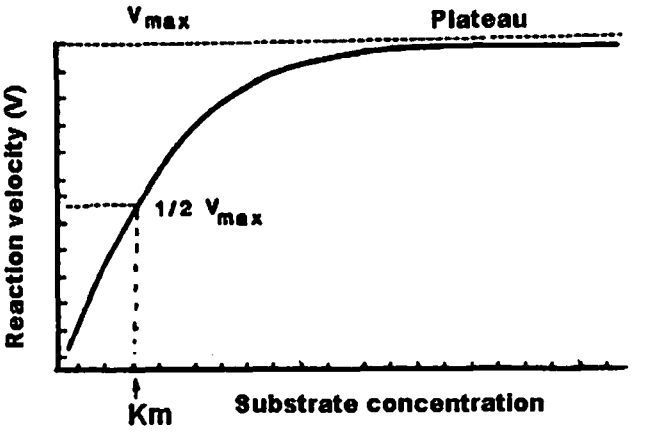
4) Michaelis and Menten equation describes how reaction velocity varies with substrate concentration as follows:

$$V_i = \frac{V_{max}\,[S]}{K_m + [S]}$$

**Where** $V_i$ = **Initial reaction velocity**
$V_{max}$ = **maximal velocity**
$K_m$ = **Michaelis constants = (k1 + K2)/k-1**
[S] = **Substrate concentration**

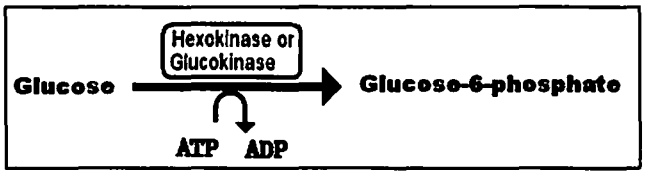
*c)* **Michaelis constant (Km):**

1) From the above equation, when substrate concentration [S] is equal to $K_m$, thus ***Km can be defined as:*** **substrate concentration that produces half maximum velocity.**

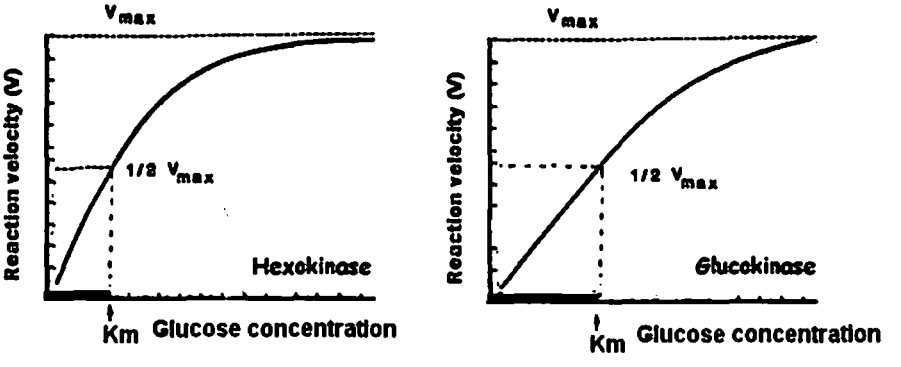



*d)* **Important conclusions about Michaelis-Menten kinetics:**

1) Substrates are usually present in physiological fluids in amounts nearly equal to $K_m$ values.
2) $K_m$ is a constant characteristic of an enzyme and its particular substrate. $K_m$ reflects the affinity of the enzyme for the substrate.
3) **The smaller the $K_m$ value, the more active the enzyme:**
   - i- Small (low) $K_m$ reflects a high affinity of the enzyme for substrate i.e. low concentration of substrate is needed to half saturate the enzyme.
   - ii- Large (high) $K_m$ reflects a low affinity to the enzyme for substrate i.e. high concentration of substrate is needed to half saturate the enzyme.
   - iii- **Example:**



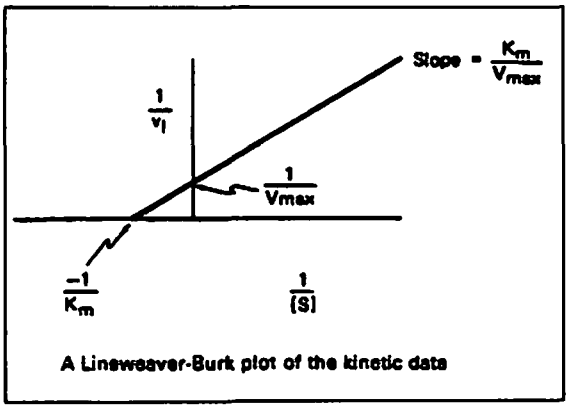

- Hexokinase is more active than glucokinase because the amount of glucose (substrate) needed to produce ½ $V_{max}$ in case of hexokinase is less than in case of glucokinase i.e. $K_m$ of hexokinase is less than glucokinase.




**The smaller the the $K_m$ value, the more active the enzyme**

*e)* **Lineweaver-Burke plot:**

1) Here, the reciprocal of V i.e. 1/V is plotted versus the reciprocal of S i.e. 1/S.
2) The curve is a straight line.
3) The curve is more practical to estimate $K_m$ because a few enzymes give the saturation curve.

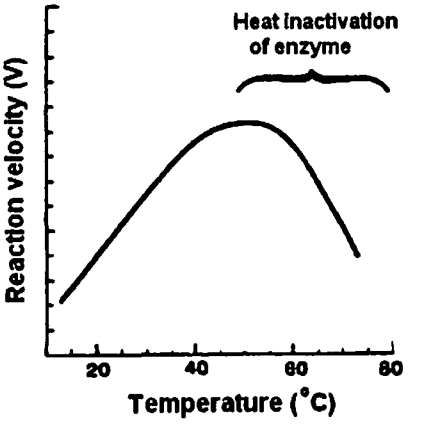


A Lineweaver-Burk plot of the kinetic data

## 3. Effect of temperature:

*a)* The optimal temperature for enzymatic activity in human body is 37 °C i.e. the temperature of the cells.

*b)* At zero temperature, the enzyme is inactive. The reaction velocity increases with increase of temperature until a maximum velocity is reached. The velocity is almost doubled every 10 °C.



**Effect of temperature on an enzyme-catalyzed reaction.**

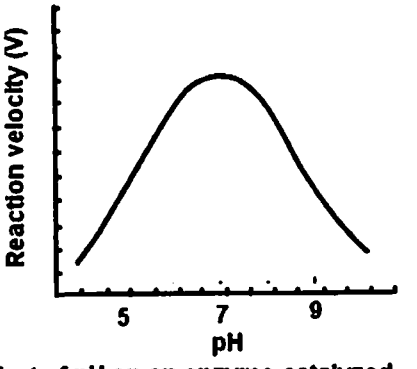
- This increase in reaction velocity is due to the increased number of molecules having sufficient energy to pass over the energy barrier and form the products of the reaction.

*c)* Further elevation of the temperature results in a decrease in reaction velocity. At 55°C - 60°C, most enzymes are denaturated and become permanently inactive.

## 4. Effect of pH:

*a)* The optimal pH for enzyme activity is that pH at which the enzyme acts maximally.

*b)* Above or below this pH, the ionic state of both enzyme and substrate will be changed, and the rate of reaction will therefore decline.



**Effect of pH on an enzyme-catalyzed reaction**

*c)* Each enzyme has its own optimal pH e.g. pancreatic lipase 7.5.

*d)* Extremes of pH can also lead to denaturation of the enzyme.

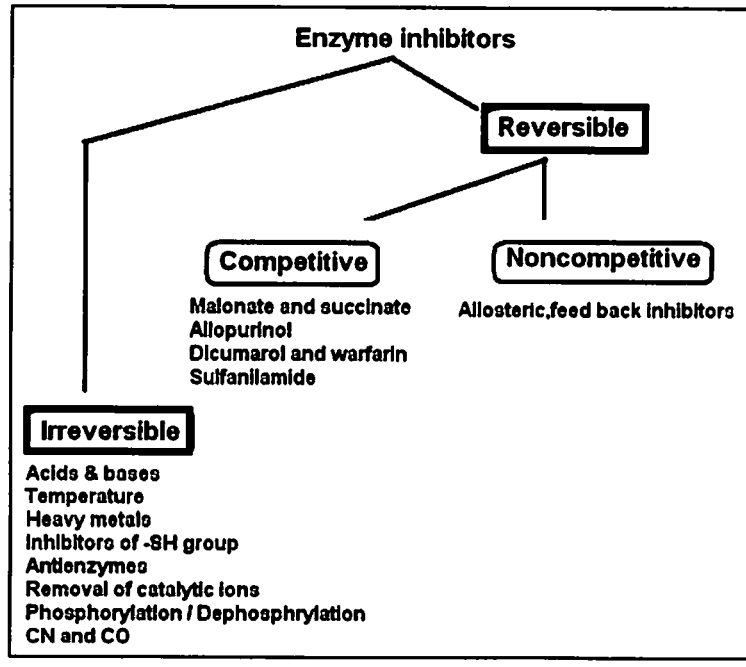
5. **Enzyme activators**: Certain substances may be needed to activate the enzymes. They include:
   *a)* **Metal ions:** e.g. chloride ions activate salivary amylase and calcium ions activate blood clotting enzymes.
   *b)* **Enzymes:** Some inactive enzymes (zymogens) may need other enzymes for activation. This includes:
      1) **Autoactivation** e.g. pepsinogen $\xrightarrow{\text{Pepsin}}$ pepsin.
      2) **Other enzymes** e.g. trypsinogen $\xrightarrow{\text{Enteropeptidase}}$ trypsin

   *c)* **HCl:** It starts activation of pepsinogen into pepsin.
   *d)* **Bile slats:** Activate pancreatic lipase enzyme.
6. **Enzyme inhibitors:** See below.

# *Enzyme inhibitors*

These are substances that can diminish the velocity of enzymatic reactions.

*The inhibition of enzymes can be classified either as reversible or irreversible*

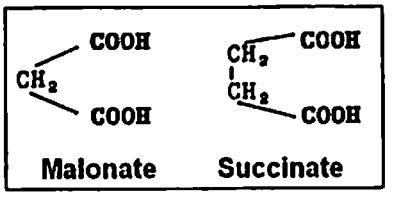


I. ***Reversible inhibitors:*** These inhibitors bind to enzymes through non covalent bonds.

- Dilution of the enzyme-inhibitor complex results in dissociation of the reversibly bound inhibitor and recovery of enzyme activity.
- Reversible inhibition may be competitive , non competitive and uncompetitive..

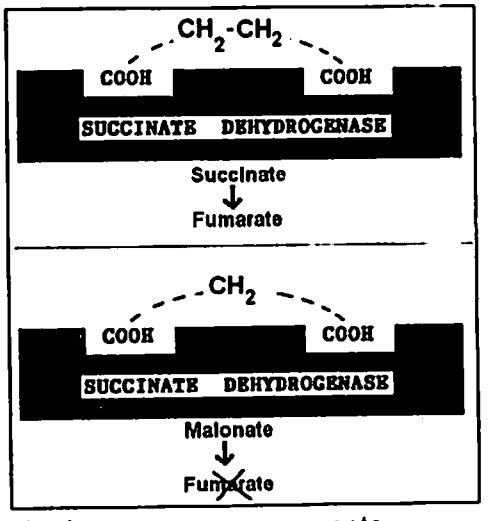
A. **Competitive inhibitors:**

1. **Definition:** There is structural similarity between substrate and inhibitor. Both substrate and inhibitor compete for active site of the enzyme.



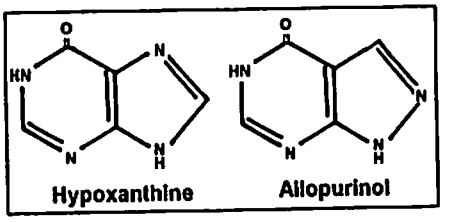

   - Both substrate (S) and inhibitor (I) can bind with the catalytic site of the enzyme to form either **Enz-S-complex** or **Enzy-I-complex**.

2. **Factors affecting the combination between enzyme and inhibitor:**



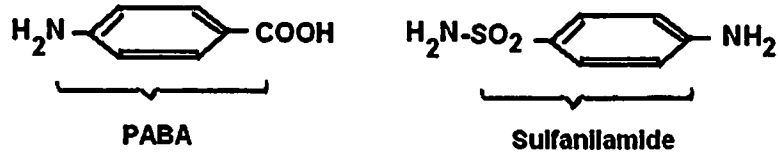

   *a)* Concentration of substrate.
   *b)* Concentration of inhibitor.
   *c)* Affinity of both inhibitor and substrate to the active site of the enzyme.
   *d)* Competitive inhibition is reversible and can be removed by adding excess substrate.

3. **Examples of competitive inhibitors:**
   *a)* **Malonate and succinate:** This is the classic example of competitive inhibition. **Succinate dehydrogenase** enzyme acts on succinate and converts it to fumarate. It is competitively inhibited by malonate.
   *b)* **Allopurinol:** It is used in treatment of gout (hyperuricemia). Allopurinol is similar in structure to hypoxanthine. It inhibits xanthine oxidase, that oxidizes hypoxanthin into xanthine then to uric acid (see nucleotide metabolism, part III).




   *c)* **Dicumarol and Warfarin:** Both act as anticoagulant because they are structurally similar to vitamin K. They act as inhibitors of **epoxide reductase** enzyme (see vitamin K).

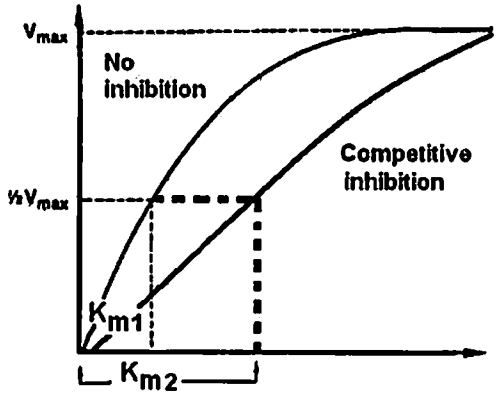
*d)* **Sulfanilamide and p-aminobenzoic acid (PABA):** PABA is required for synthesis of folic acid in bacteria. Folic acid is essential for bacterial growth and multiplication. Sulfanilamide acts as competitive inhibitor for enzyme system that uses PABA for synthesis of folic acid and acts as antibacterial drug.



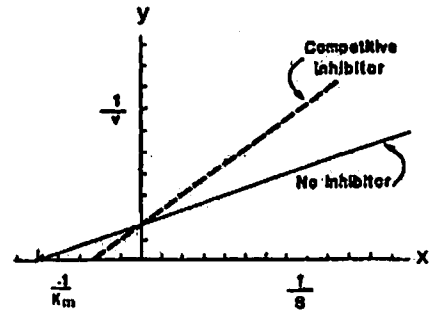

PABA Sulfanilamide

4. **Effect of competitive inhibitor on $V_{max}$ and $K_m$:**
   ($V_{max}$: not affected, Km: increased)

*a)* **Effect on $V_{max}$:** A competitive inhibition does not affect $V_{max}$ as increasing of the substrate concentration makes the reaction velocity reaches the $V_{max}$.




Substrate concentration [S]




Lineweaver-Burk plot of competitive inhibition of an enzyme

*b)* **Effect on $K_m$:**

*A competitive inhibition increases the $K_m$ of substrate* i.e. in the presence of a competitive inhibitor more substrate is needed to reach ½ $V_{max}$.

*c)* **Effect of competitive inhibitor on Lineweaver-Burke plot:**

- Vmax is unchanged
- Km is increased

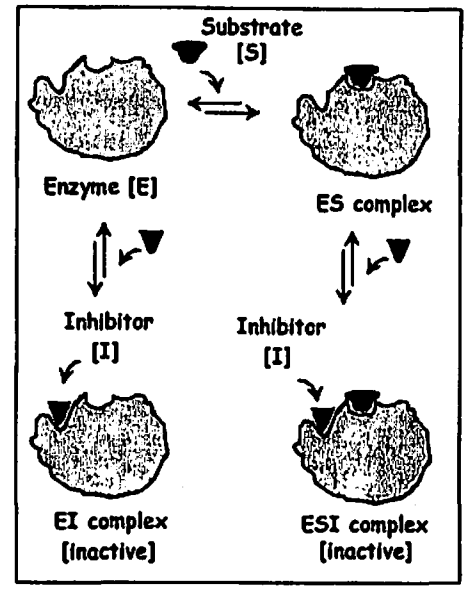
## B. Non-competitive inhibitors:

1. **Definition:** This type of inhibition occurs when the inhibitor and substrate bind to different sites on the enzyme.
2. **Characters of the combination of enzyme and inhibitor:**

*a)* The inhibitor does not alter the catalytic site.

*b)* There is no structural similarity between substrate and inhibitor.

*c)* The inhibitor can bind either free enzyme or the enzyme-substrate complex. Both enzyme inhibitor complex and enzyme substrate inhibitor complex are inactive.




3. **Examples of noncompetitive inhibitors:**

*a)* Allosteric inhibitors (see regulation of enzyme activity)

*b)* Feedback inhibitors (see regulation of enzyme activity)

4. **Effect of noncompetitive inhibitor on $V_{max}$ and $K_m$:**

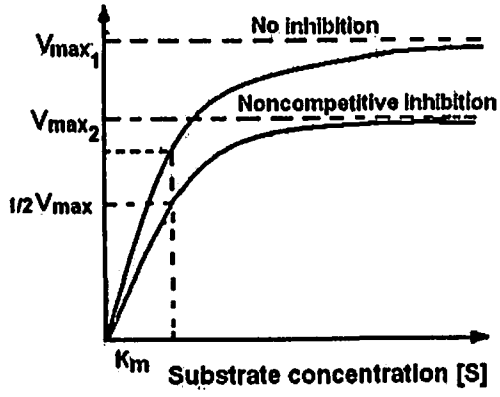
($V_{max}$: decreased, Km: not affected)

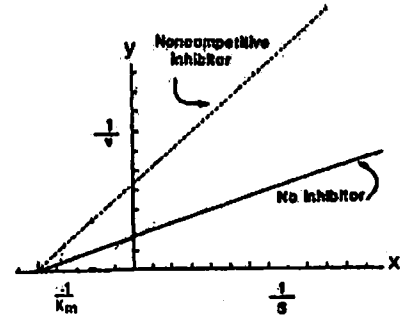
*a)* **Effect of noncompetitive inhibitors on $V_{max}$:** Non competitive inhibition cannot be overcome by increasing the concentration of substrate. Thus, noncompetitive inhibitors decrease the $V_{max}$ of the reaction.

*b)* **Effect on $K_m$:** Noncompetitive inhibitors do not interfere with the binding substrate to enzyme. Thus, the enzyme shows the same $K_m$ in the presence and absence of the noncompetitive inhibitor.

*c)* **Effect on Line weaver-Burke plot:**

- $V_{max}$ decreases
- $K_m$ is unchanged.




Lineweaver-Burk plot of noncompetitive inhibition of an enzyme

## II. *Irreversible inhibitors:*

A. This type of inhibition cannot be reversed by adding more substrate.

B. The inhibitor alters the catalytic site, preventing combination of enzyme and its substrate.

C. Irreversible inhibitors include the following:

1. **All compounds that produce precipitation or Denaturation of proteins:** as strong acids, alkalies, high temperature, repeated freezing and thawing and detergents.
2. **Inhibitors of sulfhydryl group (-SH):** sulfhydryl group is important group in the catalytic site of many enzymes. Inhibitors of the –Sh group include:
   *a)* Oxidizing agent e.g. $H_2O_2$.
   *b)* Salts of heavy metals as mercury.
3. **Antienzymes:** compounds that bind to enzyme and inactivating it e.g.:
   *a)* **Antithrombin III:** This is activated by heparin and prevents blood clotting.
   *b)* **Antiproteinases:** as α1-antitrypsin. They inhibit some enzymes that destroy proteins as elastase enzyme.
4. **Removal of catalytic ions:** Addition of EDTA to blood prevents blood clotting by removal of calcium ions.
5. **Inhibition by phosphorylation and dephosphorylation (covalent modification):** discussed later in regulation of enzyme activity.
6. **Cyanide and carbon monoxide:** They bind with iron of heme present in cytochrome oxidase enzyme. This leads to loss of enzyme function.

# Summary of factors affecting enzyme activity

**A. Velocity of reaction:** It is the increase in the concentration of product (or decrease in concentration of substrate) with time.

1. ***Initial velocity (Vi):*** **It is the initial portion of the reaction where an increase in the concentration of the product is correlated constantly with time.**
2. ***The units of velocity:*** is concentrations of the product per unit time, e.g. micromoles / minute.

**B. *Factors affecting enzyme activity:***

1. **Concentration of enzyme:** The initial velocity of a reaction is directly proportional to the amount of the enzyme present, provided that all other conditions remain constant.
2. **Concentration of substrate:**
   The initial velocity of a reaction is directly proportional to the amount of substrate present till it reaches a maximum point known as **maximum velocity ($V_{max}$)**, where any further increase in the amount of substrate causes no increase in the velocity of the reaction. This is true if all other conditions especially enzyme concentration remain constant.
   *a)* **Definition of maximum velocity($V_{max}$):** It is the maximum point in substrate velocity curve where any further increase in the amount of substrate causes no increase in the velocity of the reaction.

*b)* **Michaelis-Menten Equation:**

1) This equation describes the dependence of reaction velocity on substrate concentration.

*c)* **Michaelis constant=Km**

1) **It is substrate concentration that produces half maximum velocity.**

2) **The smaller the $K_m$ value, the more active the enzyme and vice versa.**

*d)* **Lineweaver-Burke plot:**

1) Here, the reciprocal of V i.e. 1/V is plotted versus the reciprocal of S i.e. 1/S.

2) The curve is a straight line.

3. **Effect of temperature:**

*a)* The optimal temperature for enzymatic activity in human body is 37 °C i.e. the temperature of the cells.

*b)* At zero temperature, the enzyme is inactive. The reaction velocity increases with increase of temperature until a maximum velocity is reached.

*c)* Further elevation of the temperature results in a decrease in reaction velocity. At 55°C - 60°C, most enzymes are denaturated and become permanently inactive.

4. **Effect of pH:**

*a)* The optimal pH for enzyme activity is that pH at which the enzyme acts maximally.

*b)* Above or below this pH, the ionic state of both enzyme and substrate will be changed, and the rate of reaction will therefore decrease.

*c)* Each enzyme has its own optimal pH e.g. pancreatic lipase 7.5.

*d)* Extremes of pH can also lead to denaturation of the enzyme.

5. **Enzyme activators:** Certain substances may be needed to activate the enzymes. They include:

*a)* **Metal ions:** e.g. chloride ions activate salivary amylase and calcium ions activate blood clotting enzymes.

*b)* **Enzymes:** Some inactive enzymes (zymogens) may need other enzymes for activation. This includes:

1) **Autoactivation** e.g. pepsinogen $\xrightarrow{\text{Pepsin}}$ pepsin.

2) **Other enzymes** e.g. trypsinogen $\xrightarrow{\text{Enteropeptidase}}$ trypsin

*c)* **HCl:** It starts activation of pepsinogen into pepsin.

*d)* **Bile slats:** Activate pancreatic lipase enzyme.

*e)* **Enzyme inhibitors:** see.

## Summary of Enzyme inhibitors

I. **Definition:** These are substances that can diminish the velocity of enzymatic reactions. The inhibition of enzymes can be classified either as reversible or irreversible.

**II. *Reversible inhibitors:*** These inhibitors bind to enzymes through non covalent bonds.

1- Dilution of the enzyme-inhibitor complex results in dissociation of the reversibly bound inhibitor and recovery of enzyme activity.

2- Reversible inhibition may be competitive and non competitive..

**A. *Competitive inhibitors:***

1. **Definition:** There is structural similarity between substrate and inhibitor. Both substrate and inhibitor compete for active site of the enzyme.
   *a)* Both substrate (S) and inhibitor (I) can bind with the catalytic site of the enzyme to form either Enz-S-complex or Enzy-I-complex.
   *b)* Competitive inhibition is reversible and can be removed by adding excess substrate.
2. **Factors affecting the combination between enzyme and inhibitor:**
   *a)* Concentration of substrate.
   *b)* Concentration of inhibitor.
   *c)* Affinity of both inhibitor and substrate to the active site of the enzyme.
3. **Examples of competitive inhibitors:**
   *a)* Malonate and succinate: both compete for the catalytic site of succinate dehydrogenase enzyme.
   *b)* Allopurinol and hypoxanthine: both compete for the catalytic site of xanthine oxidase enzyme, that oxidizes hypoxanthin into xanthine then to uric acid..
   *c)* Dicumarol & Warfarin and vitamin K: both compete for the catalytic site of epoxide reductase enzyme Both act as anticoagulant because they are structurally similar to vitamin K.
   *d)* Sulfanilamide and p-aminobenzoic acid (PABA): PABA is required for synthesis of folic acid in bacteria. Folic acid is essential for bacterial growth and multiplication. Sulfanilamide acts as competitive inhibitor for enzyme system that uses PABA for synthesis of folic acid and acts as antibacterial drug.
4. **Effects of competitive inhibitor on $V_{max}$ and $K_m$:**
   *a)* Effect on $V_{max}$: A competitive inhibition does not affect $V_{max}$.
   *b)* Effect on $K_m$: *A competitive inhibition increases the $K_m$ of substrate.*

**B. *Non-competitive inhibitors:***

1- **Definition:** This type of inhibition occurs when the inhibitor and substrate bind to different sites on the enzyme.

2- **Characters of the combination of enzyme and inhibitor:**
   a. The inhibitor does not alter the catalytic site.
   b. There is no structural similarity between substrate and inhibitor.
   c. The inhibitor can bind either free enzyme or the enzyme-substrate complex. Both enzyme inhibitor complex and enzyme substrate inhibitor complex are inactive.

3- **Example of noncompetitive inhibitors:**
   a. Allosteric inhibitors (see regulation of enzyme activity)

b. Feed back Inhibitors (see regulation of enzyme activity)

4- Effect of noncompetitive inhibitor on $V_{max}$ and $K_m$:

a. Effect of noncompetitive inhibitors on $V_{max}$: $V_{max}$ is decreased..

b. Effect on $K_m$: $K_m$ is unchanged.

## III. *Irreversible Inhibitors:*

A. This type of inhibition cannot be reversed by adding more substrate.

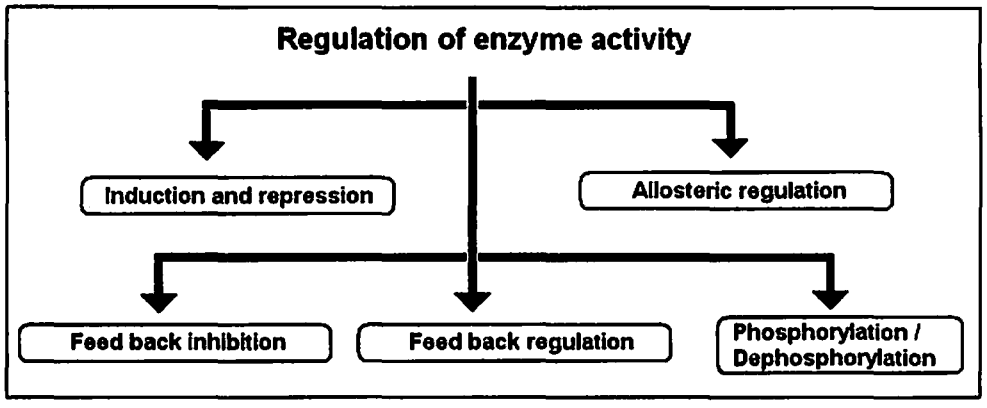
B. The inhibitor alters the catalytic site, preventing combination of enzyme and its substrate.

C. Irreversible inhibitors include the following:

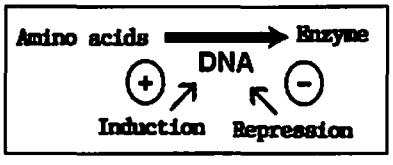
1. All compounds that produce Denaturation of proteins.
2. Inhibitors of sulfhydryl group (-SH):
3. Antienzymes: e.g.:Antithrombin III antiproteinases.
4. Removal of catalytic ions: by addition of EDTA.
5. Inhibition by phosphorylation and dephosphorylation
6. Cyanide and carbon monoxide inhibit cytochrome oxidase.

# *Regulation of enzyme activity*

Enzyme activity is regulated by many mechanisms.




## A. Induction and repression of enzyme synthesis:




1. **Rate of enzyme synthesis:** Enzyme (protein) synthesis from amino acids may be stimulated at a level of DNA by certain substances. These substances are called inducers and the process is called induction. Also enzyme synthesis may be inhibited by other substances which are called repressors and the process is called repression.

*a)* **Inducers and induction:**

1) Inducers may be **substrates** for enzymes.
2) Inducers may also be compounds similar in structure to the substrates. These compounds are called **gratuitous** inducers.
3) Inducers usually stimulate **DNA (gene)** controlling enzyme synthesis.

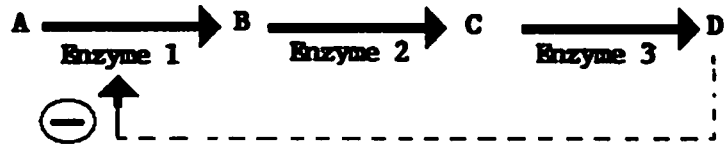
*b)* **Repressors, repression:**

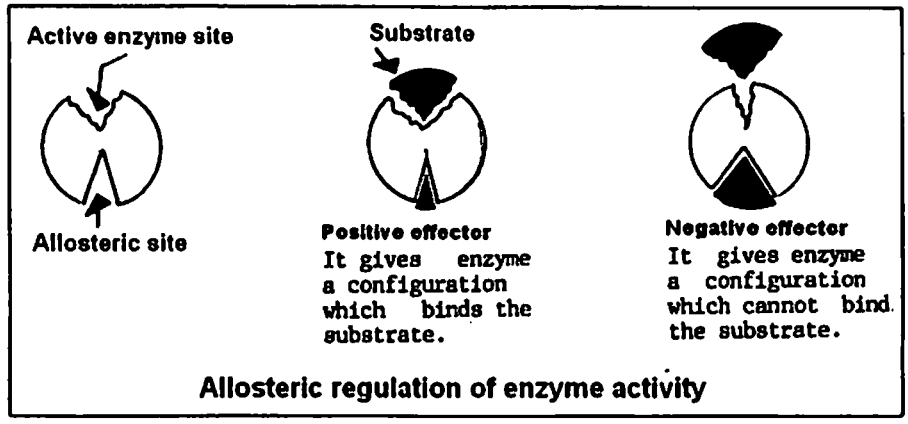
1) Repressor may be a product of metabolic pathway. It will inhibit **DNA (gene)** controlling enzyme synthesis. This called feed back regulation.

2) As a result of repression, the metabolic pathway stops, metabolic intermediates are removed and the enzyme biosynthesis again occurs. This is called **depression.**

**B. <u>Allosteric regulation of enzyme activity</u>:**

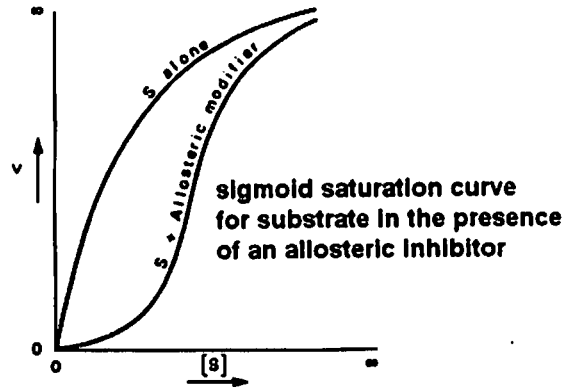
1. Allosteric enzymes generally catalyze the irreversible steps in metabolic pathways.
2. The term allosteric means "**other site**". It indicates that a molecules called **effectors** (also called **modifiers or modulators**) can bind non-covalently at a site other than active site.
   *a)* Effectors are **positive** if they stimulate catalytic reaction and **negative** if they inhibit the reaction.
   *b)* Effectors may be the end product of a metabolic pathway. If it inhibit the reaction (negative regulation),it is called: feed back inhibition.




**Allosteric regulation of enzyme activity**

3. **Classes of allosteric enzymes:** There are 2 classes of allosteric enzymes:
   *a)* **Homotropic enzymes:** in which the substrate is also the effector i.e. substrate bind to both active and allosteric site. Usually the allosteric substrate




**sigmoid saturation curve for substrate in the presence of an allosteric inhibitor**

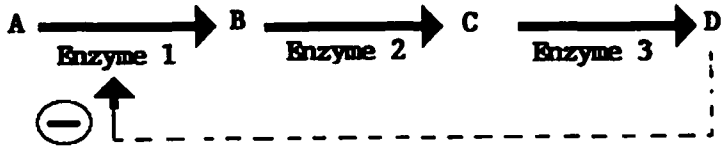
functions as a positive effector.

*b)* **Heterotropic enzymes:** in which the effector is other substance than the substrate, often the end product of the pathway.

4. **Effect of allosteric regulation on $K_m$ and $V_{max}$:**
   Allosteric regulation of enzymes causes conformational changes at the catalytic site. This leads to :
   *a)* **Altering $K_m$** for a substrate and **$V_{max}$** for the overall reaction.
   *b)* **The substrate saturation curves for allosteric inhibition often are** sigmoid. The Michaelis-Menten equation **does not** apply.

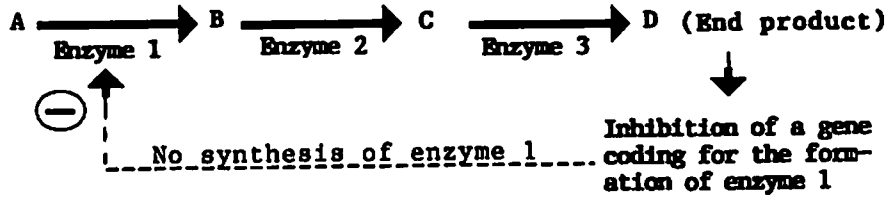
C. **Feed back inhibition:**

It means that the end product of a series of reactions directly inhibits the first enzyme of that series.




D. **Feed back regulation:**

It means that the end product of a series of reactions has no inhibitory effect on the first enzyme. It rather affects the **gene(s) that code** for the formation of that enzyme, preventing its synthesis.

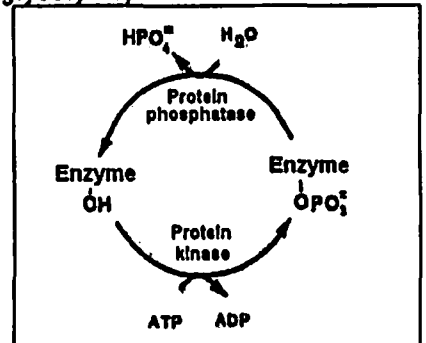



Both feed back inhibition and regulation aim to:

1. Production of any new substance just according to the body needs.
2. Removal of any harmful effects of some end products e.g. :lactic acid in anaerobic oxidation of glucose (glycolysis).

E. **Covalent modification; phosphorylation / dephosphorylation:**

1. Some enzymes may be regulated by covalent modification, by the addition or removal of phosphate groups from the enzymes.




**Covalent modification by the addition and removal of phosphate groups.**

2. Phosphorylation reactions are catalyzed by a family of enzymes, called **protein kinase.** It utilizes ATP as a phosphate donor. Phosphate groups are cleaved from phosphorylated enzymes by the action of **protein-phosphatase enzyme.**
3. Depending on the specific enzyme, the phosphorylated form may be more or less active than the unphosphorylated enzyme. For example, phosphorylation of **glycogen phosphorylase enzyme** increases activity, whereas the addition of phosphate to **glycogen synthase enzyme** results in a less active enzyme (see carbohydrate metabolism, part II).

## *Isoenzymes*

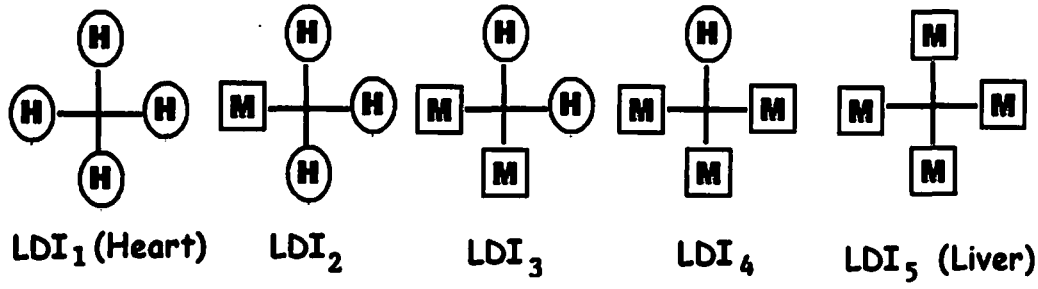
A. **Definition:**

Isoenzymes are different molecular forms of the enzyme that activate the same reaction, use the same coenzyme and same substrate but they are different in chemical protein structure. This leads to:

1. Different immunological reactions.
2. Different Km and Vmax
3. Different physical properties.

B. **Example:**

1. **Lactate dehydrogenase enzyme (LD)** is a tetramer i.e. contains 4 polypeptide chains. These 4 chains are a mixture of different proportions of 2 chains **H and M** (H after heart & M after muscle).
2. There are 5 isoenzymes of lactate dehydrogenase enzyme: $LDI_1$, $LDI_2$, $LDI_3$, $LDI_4$ and $LDI_5$.




**Lactate dehydrogenase isoenzymes** *Oraby*

C. **Diagnostic importance of isoenzymes:** Determination of different isoenzymes helps in diagnosis of diseases e.g.

1. Serum $LDI_1$ increases in certain heart diseases (myocardial infraction).
2. Serum $LDI_5$ increases in certain liver diseases (infective hepatitis).

***Enzymes in clinical diagnosis*:** See blood, body fluids, part III.

# Chapter 6 *Vitamins*

## I. *DEFINITIONS:*

**A. Vitamins:** Are organic compounds that:

1. Essential for many biochemical reactions.
2. Many of them act as coenzymes.
3. They do not enter in the structure of the tissues or oxidized by them.
4. They are needed in very small amounts.

**B. Provitamins:**

These are precursors of vitamins that converted into vitamins inside the body e.g. carotenes are provitamin A.

**C. Vitamers:**

These are different forms of one vitamin e.g. Vitamin D has 2 vitamers; $D_2$ and $D_3$.

## II. *CLASSIFICATION OF VITAMINS:* According to the solubility, vitamins are classified into:

**A. Fat soluble vitamins:** These are vitamins: **D, E, K and A.**

1. They are soluble in fat solvents.
2. They need bile salts for absorption.
3. They can be stored in the body.

**B. Water soluble vitamins:** These are vitamins: **C and B complex group.**

1. They are soluble in water
2. Most of them are not stored in the body.

# *FAT SOLUBLE VITAMINS*

## I. *Vitamin A (retinoids):*

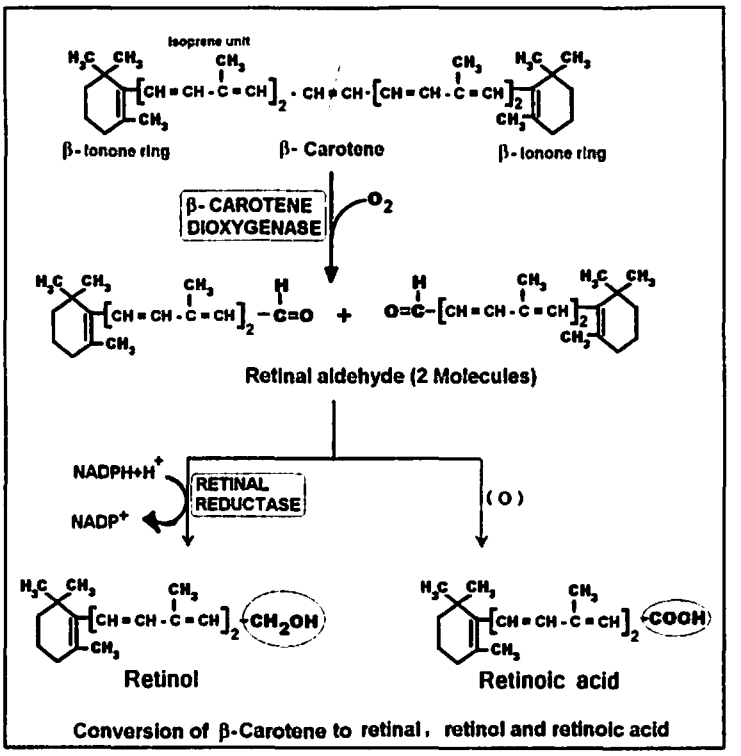
**A. Structure:**

1. Carotenes are the provitamin A.
2. Retinol, retinal and retinoic acid are the forms (vitamers) used by the body.

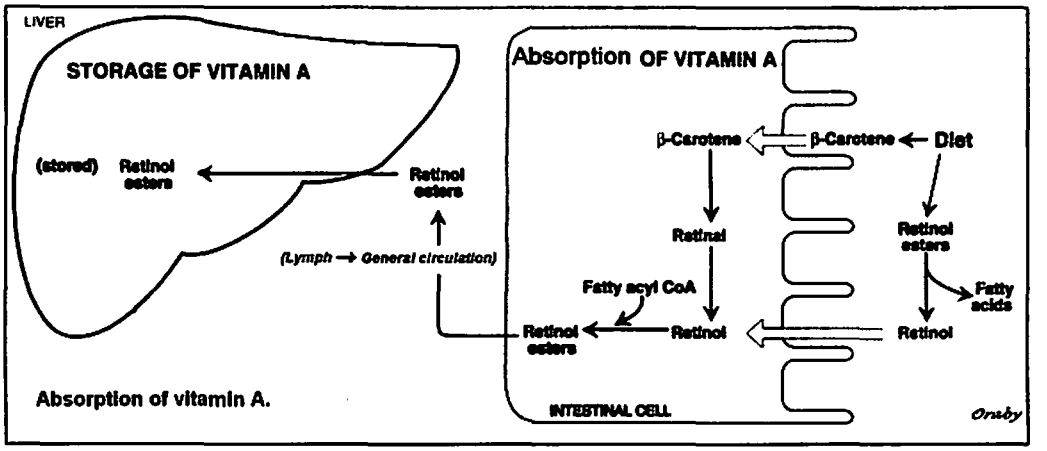
**B. Sources:**

1. **Animal sources:**
   *a)* Liver, eggs and milk fat.
   *b)* Fish liver oils e.g. shark liver oil.

2. **Plant sources:**
   *a)* Vitamin A is present in plants as carotenes (= provitamin A).
   *b)* **Carotenes (α, β and γ):**
      1) Present in carrots, potato and tomatoes.
      2) Carotenes are yellow pigments containing β-ionone ring at one end of the molecule.
      3) Carotenes are converted into vitamin A (retinal aldehyde) in the intestine.




## C. Absorption and storage:

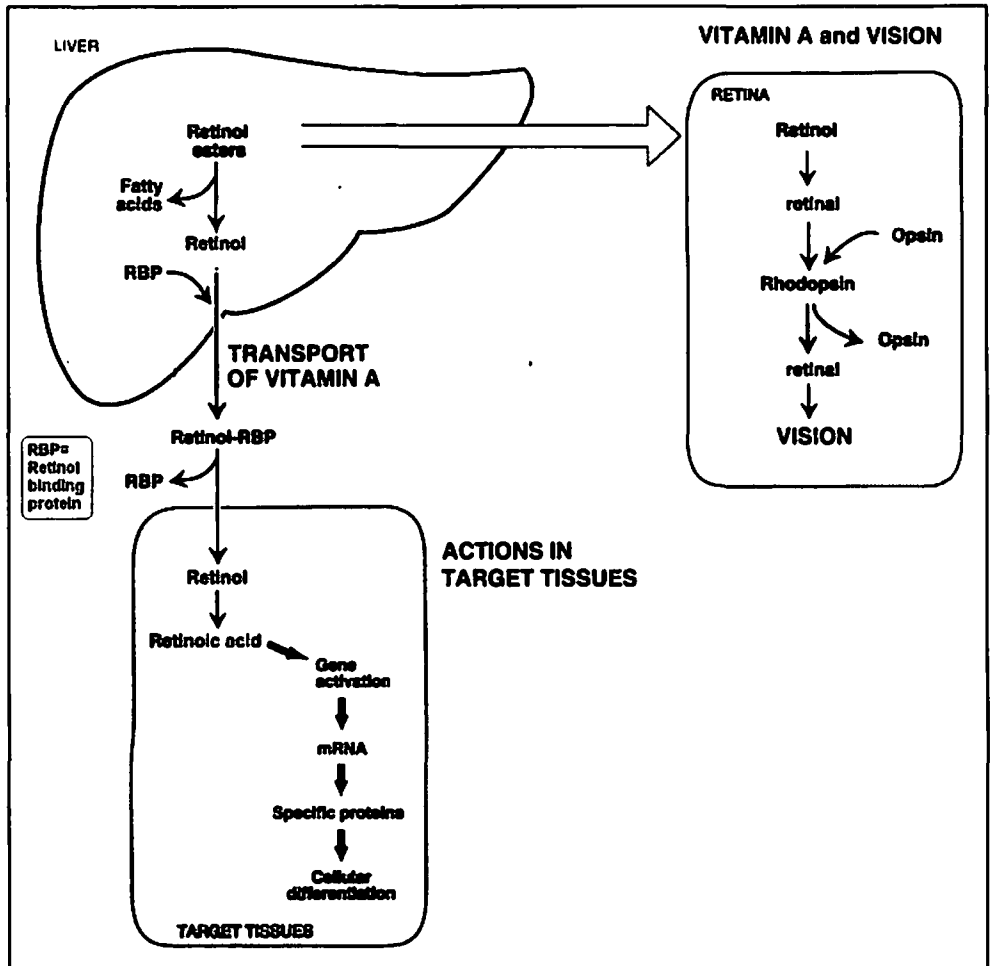



1. Diet contains retinol esters and β-carotene.
2. Retinol esters are hydrolyzed into fatty acids and retinol that absorbed into intestinal mucosal cells.

3. β-carotene is absorbed and converted into retinal (by β-carotene dioxygenase enzyme). Retinal then converted into retinol.
4. In the intestinal mucosal cells, retinol re-esterifies with fatty acid to form retinol ester.
5. Retinol esters are absorbed through lymph vessels into general circulation and transported to the liver, where 90% of the body's vitamin A is stored.

**D. Metabolism:**

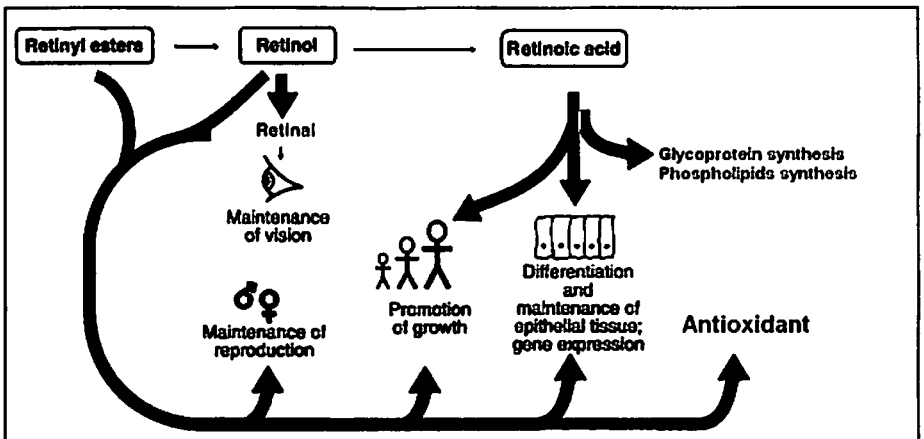
1. When the body cells need vitamin A, stored retinol esters are hydrolyzed and free retinol combines with a protein formed by the liver called **retinol binding protein** (RBP). **RBP** carries retinol to the retina and target cells.
   *a)* In retina, retinol is converted into retinal that essential for visions.
   *b)* In other target cells retinol is oxidized into retinoic acid which binds to nuclear receptors. Retinoic acid receptor complexes stimulate genes. This mode of action is similar to that of hormones.




**Metabolism of Vitamin A.** *Oraby*

E. **Functions of vitamin A:** Vitamin A acts as a hormone. It binds to nuclear proteins and acts on certain genes. It has the following functions:

1. **Vision:**
   Retinal is essential for night vision (see later).
2. **Reproduction:**
   Retinol is essential for reproduction. It supports sperm formation (spermatogenesis) in males and maintains fetal life in females.
3. **Growth:**
   Retinol is essential for normal growth and bone & teeth formation.
4. **Maintenance of epithelial cells:**
   Retinol and retinoic acid are essential for normal differentiation of epithelial cells. This is important for smoothness of skin and mucus membranes. Retinol is also essential for intact cornea.
5. **Retinoic acid:** is important for
   *a)* **Glycoprotein** synthesis.
   *b)* **Phospholipids** synthesis in the lungs (lung surfactant).
   *c)* **Cell differentiation.**
6. **Antioxidant (anticancer) action:**
   *a)* Retinoids and carotinoids (carotenes) act as antioxidants and protect tissues from toxic effect of some oxidants that may lead to epithelial tissue cancer.




Summary of actions of retinoids.

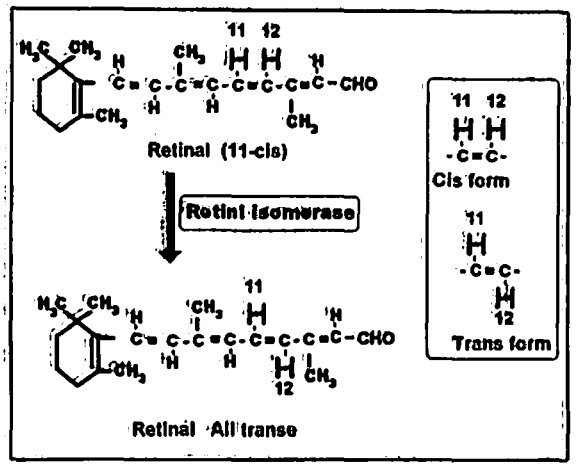
F. **Vision:**

*a)* The human retina contains two types of receptor cells for vision; cones and rods:
   1) Cone cells are responsible for day vision and color.
   2) Rod cells are responsible for vision in poor light e.g. at night.

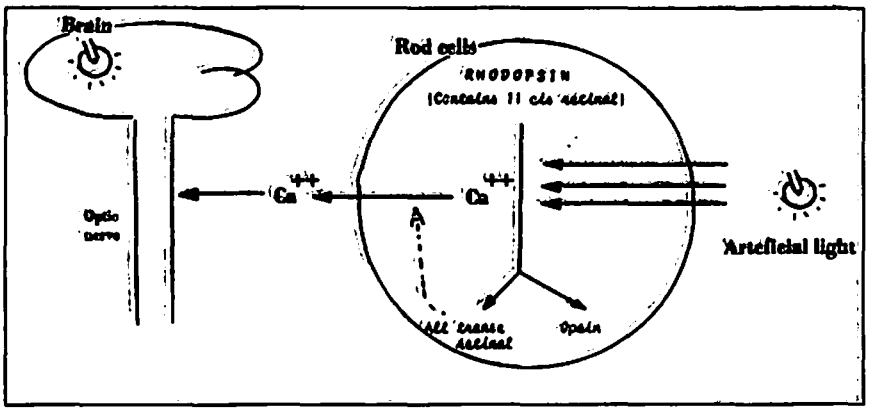
*b)* Vitamin A is a component of a visual pigment (rhodopsin) present in cones and rods.

*c)* **Visual cycle:**

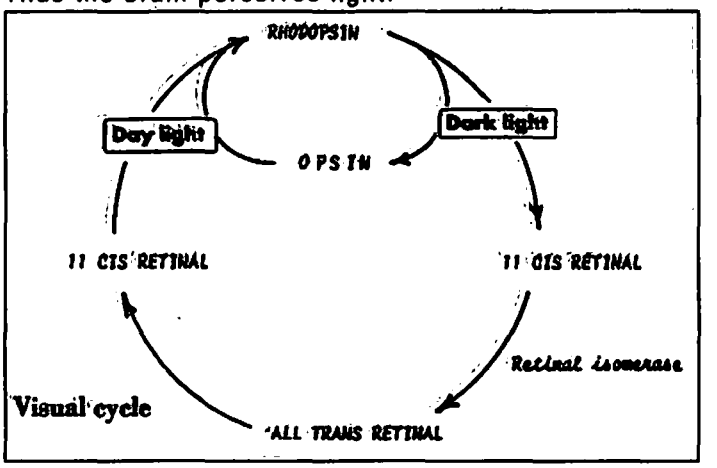
1) Rhodopsin consists of protein called opsin bound to **11-cis retinal** (double bond at position 11 is in cis form, while other double bonds are in trans form).




2) When rhodopsin is exposed to dark light, 11 cis retinal is converted into all trans retinal (all double bonds are in trans form).




3) All trans retinal changes the permeability of cell membrane of rod cells. This allows the calcium ions to pass out of the cell membrane. This stimulates the nerve impulse in optic nerve. Thus the brain perceives light.



4) For vision, rhodopsin must be regenerated. All trans retinal are converted back to 11-cis retinal.

**G. Deficiency of vitamin A:**

1. **Eye:**
   *a)* **Night blindness**: impaired dark adaptation.
   *b)* **Xero-ophthalmia**: dryness and roughness of cornea.
2. **Growth retardation.**
3. **Skin and mucus membranes**: Roughness of skin (goose skin) and mucus membranes of different body systems e.g. urinary system. This leads to infection.

**H. Requirements of vitamin A**: 5000 IU/day.

**I. Excess vitamin A (overdose or hypervitaminosis A):**

It occurs when excessive vitamin A intake exceeds the capacity of RBP. Free retinol will release in blood with the following toxic effects: ***Headache, nausea, bone pain and loss of hair.***

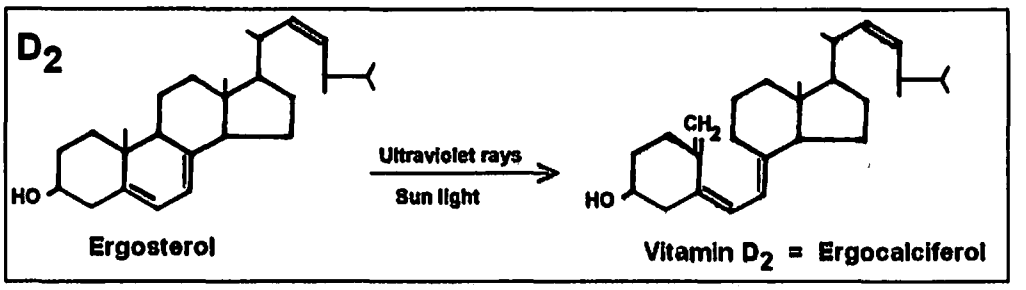
## II. *Vitamin D (calciferol):*

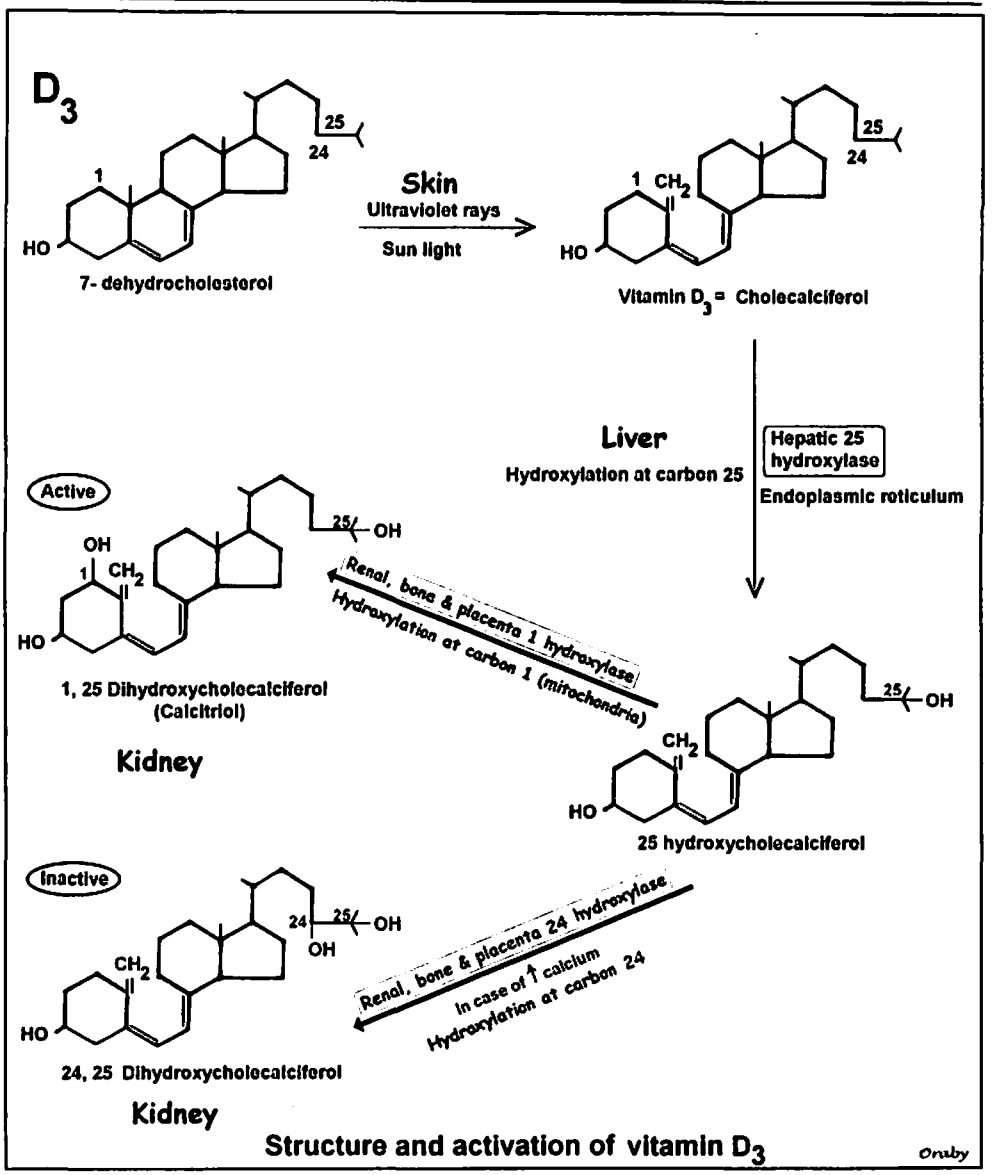
**A. Sources:**

1. Ultraviolet rays of sun generate the D vitamins from the provitamin ergosterol (in plants) and 7-dehydrocholesterol (in human and animals).
2. Liver, egg, yeast and fish liver oils are rich in vitamin D.

**B. Structure and activation of vitamin D group:**

1. Active vitamin D is a steroid hormone. It is synthesized and activated as shown in the diagram.





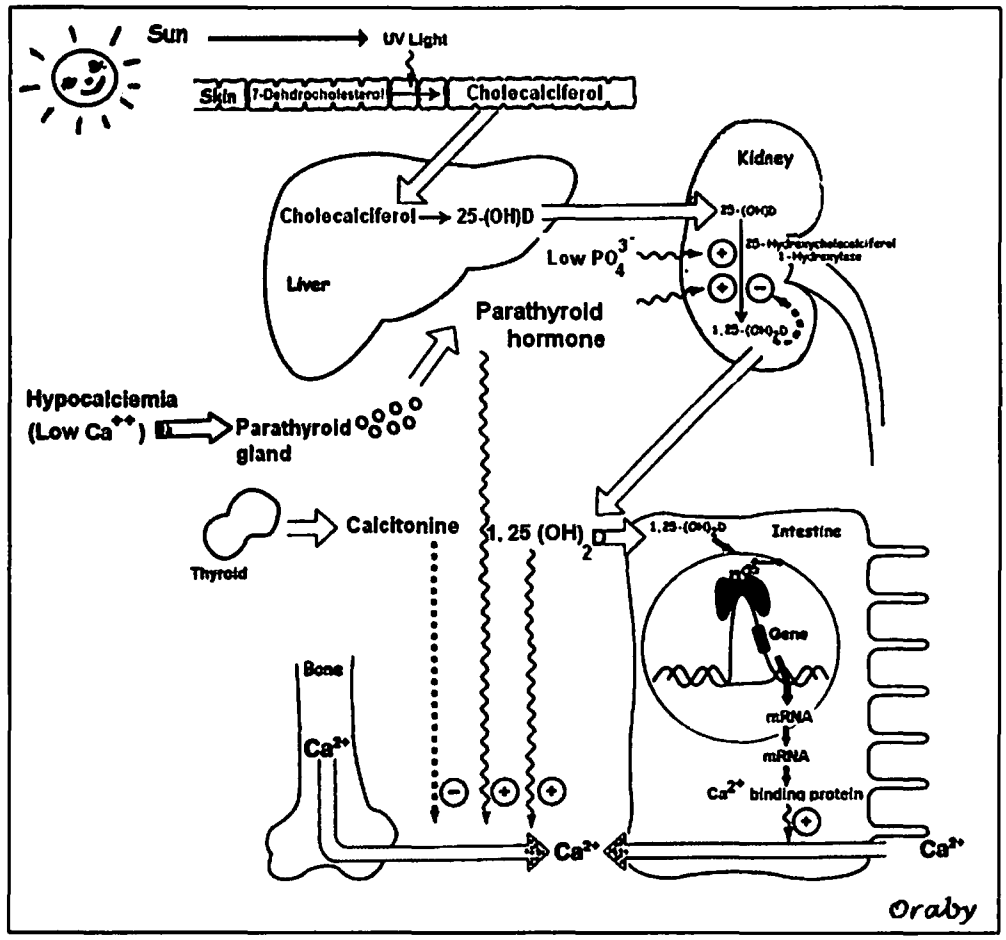

C. **Functions of vitamin D**: 1,25 dihydroxycholecalciferol (calcitriol) acts as a hormone. It has the following functions:

1. **Normalization of serum calcium:** Calcitriol maintains serum calcium level through its effects on intestine, bones and kidneys.
   *a)* **On intestine:** It stimulates synthesis of calcium binding protein (calbindin) that responsible for calcium absorption.
   *b)* **On bones:** It stimulates calcium reabsorption from bones.
   *c)* **On kidneys:** It increases renal tubular reabsorption of calcium.
2. **Mineralization of bones:**
   *a)* **In small doses:** calcitriol helps bone mineralization by providing calcium and phosphate.
   *b)* **In large doses:** The reverse occurs, where calcium and phosphate move from bone to blood.

3. **Absorption of phosphate** from intestine. It increases also tubular reabsorption of phosphate.
4. **Synthesis of osteocalcin:**
   *a)* It is calcium binding protein present in bones.
   *b)* It is important for proper mineralization of bones.
   *c)* $1,25(OH)_2D_3$ stimulates its synthesis in the form of pro-osteocalcin.

**Note**: 24, 25 dihydroxycholecalciferol is biologically inactive.

**D. Regulation and mechanism of action of 1,25 $D_3$ (calcitriol):**




1. **Hypocalcemia** → release of parathyroid hormone → Activation of renal 1 hydroxylase enzyme → Conversion 25 (OH) $D_3$ into 1,25 $(OH)_2$ $D_3$.
2. **Hypophosphatemia** → Direct Activation of renal 1 hydroxylase enzyme → Conversion of 25 $D_3$ into 1,25 $(OH)_2$ $D_3$.
3. **In the intestinal mucosal cells**, 1,25 $(OH)_2$ $D_3$ is bound to specific cytoplasmic receptors forming a complex. This complex enters the nucleus, stimulating DNA to produce specific mRNA. This mRNA is responsible for synthesis of calcium binding protein (calbindin), which helps the absorption of calcium.

4. **Absorption of phosphate** is similar to the previous mechanism but it occurs secondary to calcium absorption.

E. **Deficiency of vitamin D:** Causes demineralization of bones that leads to rickets and osteomalacia:
   1. **Rickets in children:** characterized by bone deformities.
   2. **Osteomalacia in adults:** characterized by bone fractures.
   3. **Renal rickets:** In chronic renal failure there is a deficient formation of active form of the vitamin $D_3$ (decreased 1 hydroxylation of the vitamin). This leads to ***renal rickets***.

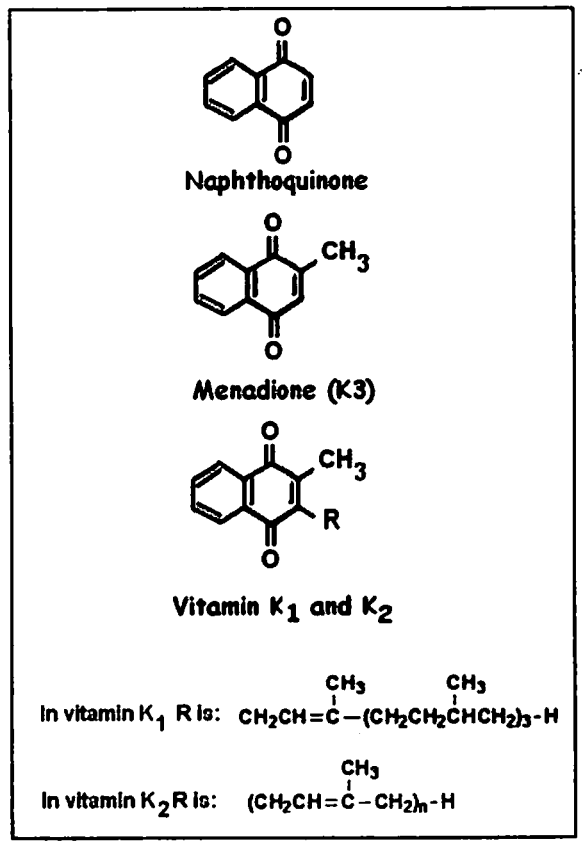
F. **Requirements:** 400 IU/day

G. **Excess vitamin D ( overdose or hypervitaminosis D):**
   1. This leads to abnormal calcification of tissues and deposition of calcium and phosphate in different systems e.g. renal stones.

## III. *Vitamin K :*

A. **Structure:** There are three forms (vitamers) of vitamin K: $K_1$, $k_2$ and $K_3$.
   1. The difference between K1 and $k_2$ lies in side chain R.
   2. $K_3$ is synthetic vitamin and has no R side chain.

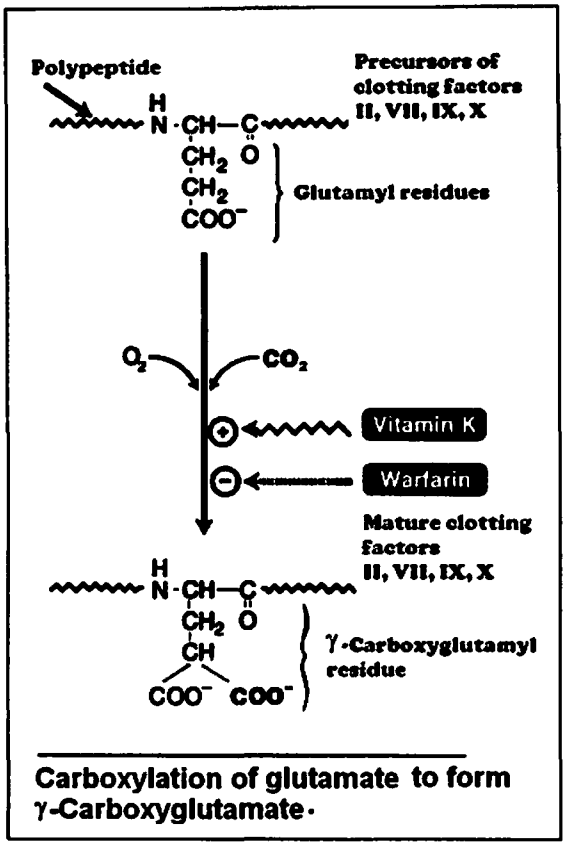
B. **Sources:**
   1. The main source of vitamin K is the intestinal bacteria. They produce Vitamin $K_2$.
   2. Vitamin $K_1$ is present in plants.
   3. Vitamin $K_3$ is synthetic. It is water soluble and more potent than vitamin $K_1$ & $K_2$.




C. **Functions of vitamin K :**
   1. Synthesis of some blood clotting factors in liver: prothrombin (factor II), and factors VII, IX and X.
   2. Synthesis of osteocalcin (calcium binding protein) in bones.

## D. Mechanism of vitamin K action:

1. Prothrombin is a protein formed in the liver as inactive form called prothrombin precursor. It contains 10 glutamic acid residues.
2. Carboxylation of these glutamic acid residues into γ-carboxy glutamate converts the molecule into active thrombin.
3. The same carboxylation reactions occur to factors VII, IX and X.




**Carboxylation of glutamate to form γ-Carboxyglutamate.**

## E. Deficiency of vitamin K:

1. It leads to **impairment of blood clotting.**
2. Deficiency of vitamin K is rare because intestinal bacteria synthesize it.
3. **Vitamin K deficiency occurs in the following conditions:**
   - *a)* **New born infant** because their intestine is sterile.
   - *b)* Long use of **antibiotics** as they kill intestinal bacteria.
   - *c)* **Liver diseases:**
     1) liver is the site for prothrombin synthesis.
     2) Liver forms bile salts which are essential for vitamin K absorption.
   - *d)* Long use of **dicumarol and warfarin** (anticoagulants) as they act as competitive inhibitors with vitamin K for its site of action.

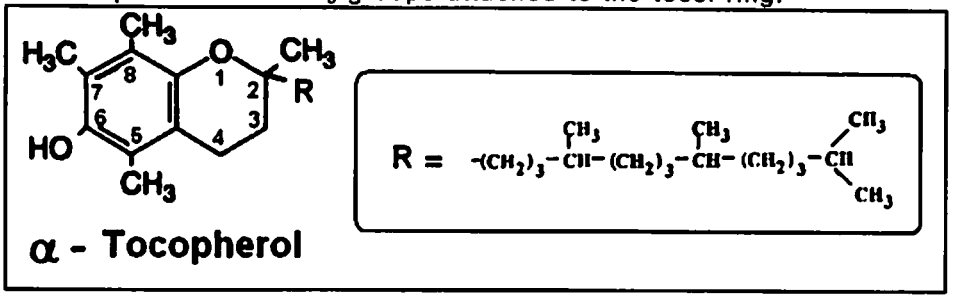
## F. Osteocalcin :

1. It is calcium binding protein present in bones.
2. It is important for proper mineralization of bones.
3. $1,25(OH)_2D_3$ stimulates its synthesis in the form of pro-osteocalcin.
4. Vitamin K converts pro-osteocalcin into active osteocalcin (by mechanism similar to that of prothrombin i.e. carboxylation of glutamic acid residues.

## IV. *Vitamin E (tocopherols) :*

### A. Structure :

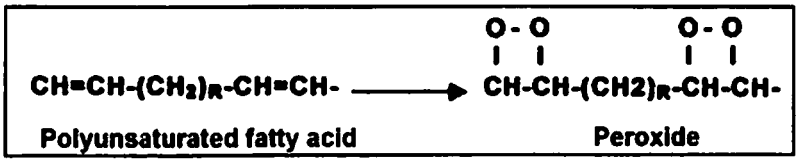
1. There are four types of tocopherols α , β , γ and δ.
2. All contain tocol ring.
3. The most active member is α tocopherol.
4. β , γ and δ tocopherols differ from α tochopherol in number and position of – $CH_3$ groups attached to the tocol ring.




### B. Sources: Vegetables and seed oils. It is present also in fish liver oils.

### C. Functions of vitamin E:

1. **Antioxidant:** Vitamin E prevent non-enzymatic oxidation of cell components (e.g. polyunsaturated fatty acids, DNA and cell membranes) by molecular oxygen or free radicals.
2. Vitamin E **removes peroxide** formation in polyunsaturated fatty acids.




3. **Protection against atherosclerosis and heart diseases:**
   *a)* Vitamin E acts as antioxidant. It prevents oxidation of LDL. Oxidized LDL causes atherosclerosis and heart disease.

### D. Deficiency: Occurs usually in premature infant :

1. **Hemolysis of RBCs** and anemia: due to lack of protection against peroxides.
2. Muscle breakdown.

### E. Requirements:

1. 15 IU/day

# Water Soluble Vitamins

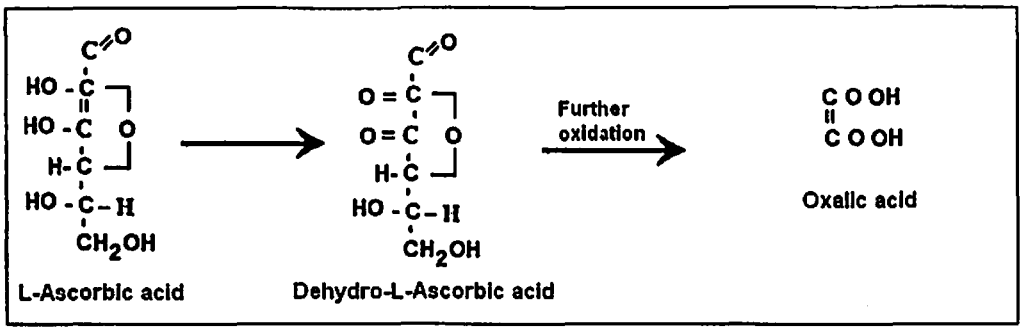
## I. Vitamin C = L-Ascorbic acid

### A. Sources:

1. Fruits especially citrus fruits (lemon, orange), melon and strawberry.
2. Vegetables especially green leafy vegetables as lettuce, tomatoes, potatoes, raw cabbage and green peppers.
3. Guava is very rich in vitamin C.

### B. Structure:

1. Animal tissues contains 90% L-ascorbic acid and 10% dehydro L-ascorbic acid. Both forms are active.
2. Further oxidation gives oxalic acid.

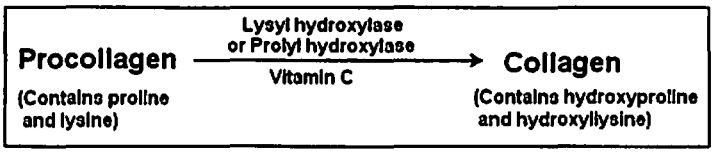



### C. Chemical properties:

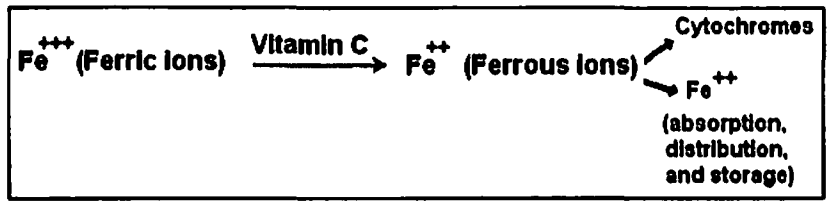
1. Ascorbic acid is acidic because it contains two enol groups (C-OH).
2. Vitamin C is the most labile vitamin in food i.e. easy to be destroyed. Much of its activity is lost through oxidation during preparation, cooking and storage.

### D. Functions of vitamin C:

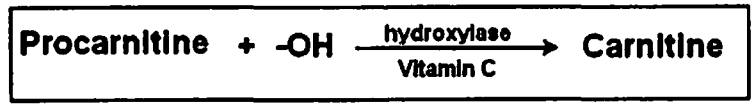
1. **Formation of collagen protein:**
   *a)* Ascorbic acid is essential for the conversion of the procollagen (immature collagen) into collagen. Procollagen is a protein containing proline and lysine. Hydroxylation of both amino acids is catalyzed by hydroxylase enzymes and by vitamin C as a coenzyme. This converts procollagen into collagen.
   *b)* Collagen is essential for the synthesis of connective tissue, bone, cartilage and teeth.



2. **Absorption and mobilization of iron:** Ascorbic acid is a potent reducing agent, keeping iron in ferrous state:




3. **Ascorbic acid acts as a coenzyme for many hydroxylase enzymes in the pathways of:**
   *a)* **Bile acids synthesis.**
   *b)* **Osteocalcin synthesis.**
   *c)* **Carnitine synthesis:** carnitine stimulates fatty acid oxidation in mitochondria.




   *d)* **Epinephrine synthesis:**
4. **Antioxidant action :**
   Vitamin C acts as antioxidant and protect tissues from toxic effect of some oxidants that may lead to cancer.

## E. Deficiency: → (scurvy):

Vitamin C store is sufficient for 3 months. If this store is depleted a disease called **scurvy** will result. It is characterized by:

1. **Manifestations due to decreased collagen formation:**
   *a)* Bleeding into gum, muscles, joints, kidneys, gastrointestinal tract and pericardium.
   *b)* Defective formation of bone and teeth.
   *c)* Defective healing of wounds.
2. **Anemia:** due to decreased absorption of iron and bleeding.
3. **Manifestations due to decreased neurotransmitters** (epinephrine and norepinephrine):
   *a)* Behavioral changes.
   *b)* Severe emotional disturbances.
4. **Manifestations due to decrease carnitine and fatty acids oxidation:**
   *a)* General weakness.

## F. Excessive vitamin C:

Intake of high doses of vitamin C produces hyperoxaluria (increased oxalate in urine) and may lead to stone formation.

**G. Requirements:**

60 mg / day.

# The B complex vitamins

## I. Introduction:

**A.** These are a group of vitamins of different chemical molecules. They are put together in one group because:-

1. All are soluble in water.
2. All are present in the same sources. B vitamins are particularly abundant in whole grain cereals, liver and yeast.
3. Due to their presence in the same foods: deficiencies of B vitamins are often multiple rather than singular.

**B. Functions of vitamin B complex:**

1. All B-complex vitamins serve as coenzymes in enzymatic reactions.
2. Folic acid and $B_{12}$ act as coenzymes in hemtopoiesis (formation of red blood cells)

**C. Absorption and storage of vitamin B complex:**

1. The B vitamins are absorbed in the intestine and transported in the portal circulation.
2. The tissue stores of most B vitamins are minimal. The depletion occurs over several weeks in response to dietary restriction or increased the requirements as in pregnancy. Body stores of folic acid and vitamin $B_{12}$ are more extensive than other B vitamins.

**D. Toxicity of vitamin B complex:**

Toxic effects are relatively uncommon, since excessive ingestion of water soluble vitamins is followed by saturation of body stores and rapid loss of excess vitamins in the urine.

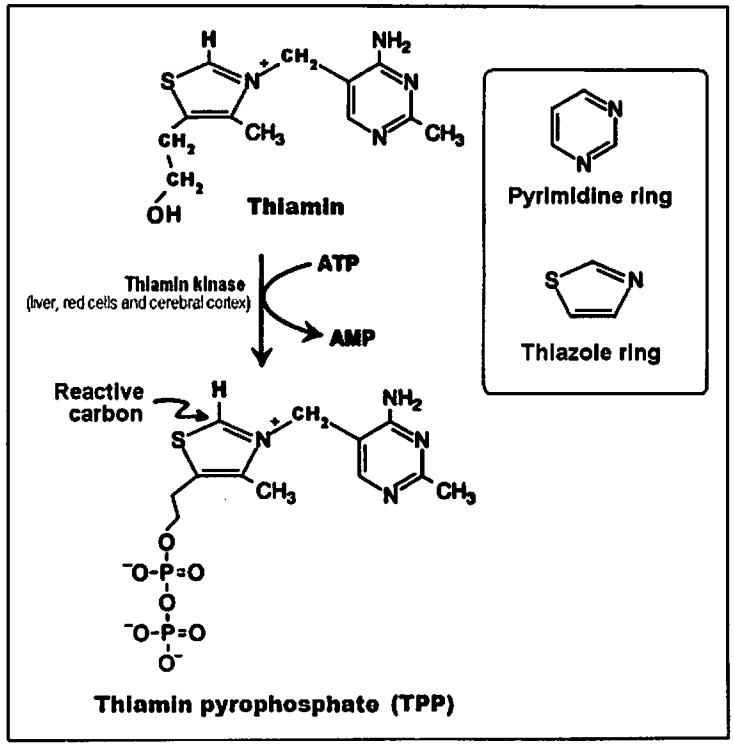
## II. Thiamin (vitamin $B_1$):

**A. Sources:**

1. Whole grain cereals, legumes, and yeast.
2. Unpolished rice and whole wheat bread.

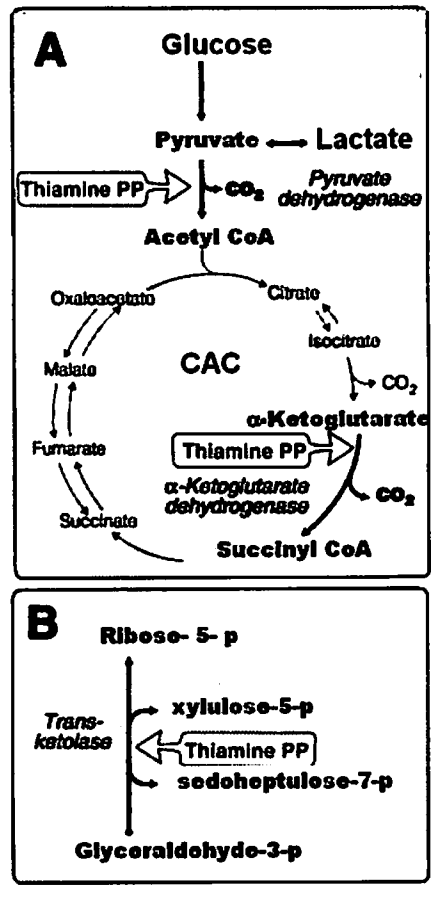
**B. Structure:**

1. Thiamin consists of a substituted pyrimidine ring connected to a substituted thiazole ring through a methylene bridge ($CH_2$).
2. **Active form of $B_1$ = Thiamin diphosphate (TPP):**
   *a)* It is also called thiamin pyrophosphate.
   *b)* Formation of TPP needs thiamin kinase enzyme, which is present in liver, red cells and nervous tissue.



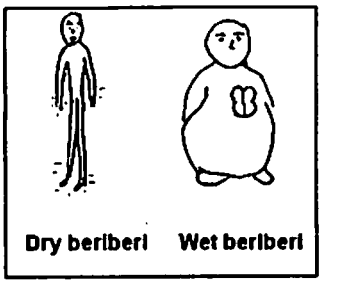

C. **Functions of B1 (TPP):** TPP acts as coenzyme in two separate reactions in carbohydrate metabolism. These are:

1. **Oxidative decarboxylation of α-ketoacids:** (pyruvate, α-ketoglutarate and ketoacids of branched chain amino acids; Valine, leucine and isoleucine) by:
   *a)* Pyruvate dehydrogenase enzyme.
   *b)* α-ketoglutarate dehydrogenase (in citric acid cycle,CAC).
   **Note:** These reactions produce energy and $CO_2$.
2. **Transketolation reactions:** by transketolase, in pentose phosphate pathway.
3. Thiamin is also essential for the process of nerve conduction and structure of nerve membrane. Thiamin triphosphate acts as phosphate donor for phosphorylation of sodium transport channel of the nerve membrane.



**D. Deficiency: → *Beriberi.***

1. ↓ TPP→Impaired carbohydrate metabolism. This leads to ↓ Energy production → Impaired cellular functions especially of nervous system → Beriberi
2. **Types of beriberi:**
   *a)* **Dry beriberi:** (and *Wernicke-Korsakoff syndrome*) characterized by:
      1) Peripheral neuritis.
      2) Muscle wasting and hyperesthesia *(sensitivity to different sensations, such as pain, heat, etc.).*
   *b)* **Wet beriberi:** characterized by:
      1) Heart failure.
      2) Edema.




**E. Requirements:** 1.5 mg / day.

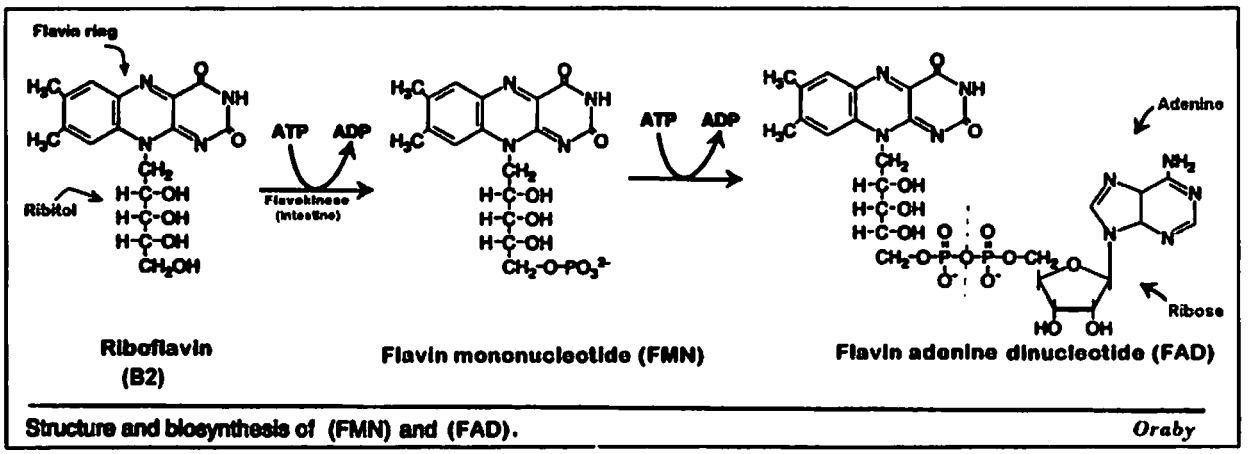
## III. *Riboflavin (vitamin $B_2$):*

**A. Sources:**

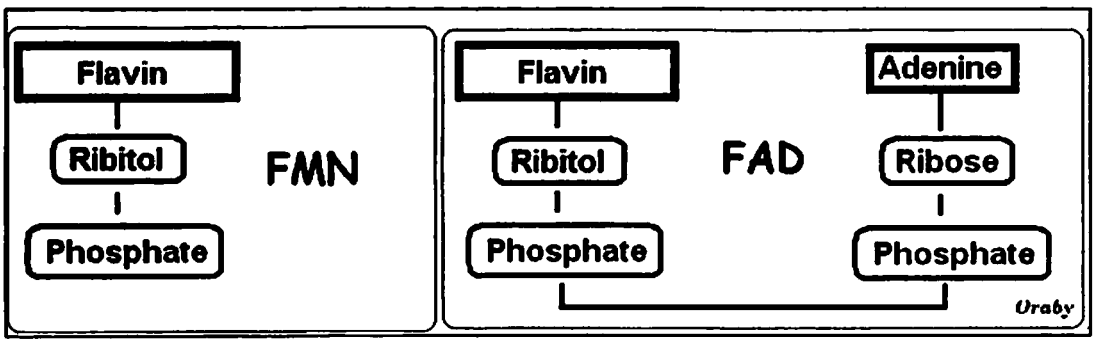
1. Milk and milk products.
2. Eggs, liver and green leafy vegetables.

**B. Structure:**

1. It is formed of flavin ring attached to ribitol (alcohol of ribose sugar).




Structure and biosynthesis of (FMN) and (FAD). *Oraby*



2. **Active forms of riboflavin:**
   *a)* Riboflavin enters in the structure of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD).
   *b)* FMN is formed by phosphorylation of riboflavin by ATP (by intestinal flaviokinase enzyme). FAD is formed by the transfer of an AMP moiety from ATP to FMN.

C. **Functions of $B_2$:**

1. Both FMN and FAD are coenzyme for flavo enzymes. They act as hydrogen (or electron) carriers in oxidation reduction reactions → $FMNH_2$ and $FADH_2$.

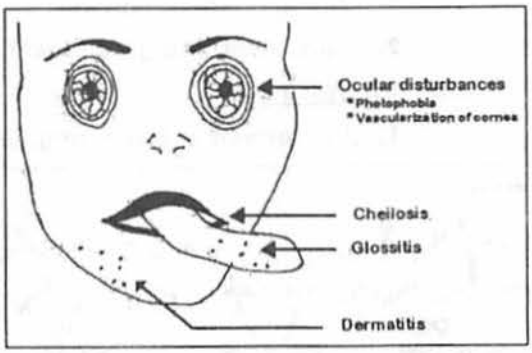
**Examples:**

**L-Amino acid + FMN** $\xrightarrow{\textit{L-Amino acid oxidase}}$ **Imino acid + $FMNH_2$**

**Succinate + FAD** $\xrightarrow{\textit{Succinate dehydrogenase}}$ **Fumarate + $FADH_2$**

D. **Deficiency:** B2 deficiency is not fatal. It is characterized by:

1. **Ocular disturbances**:
   *a)* **Photophobia** i.e. abnormal sensitiveness of the eye to the light.
   *b)* Vascularization of cornea.
2. **Cheilosis** (fissuring at the corners of the mouth).
3. **Glossitis** i.e. inflammation of tongue, which appears smooth and purplish.
4. **Dermatitis** i.e. inflammation of the skin.

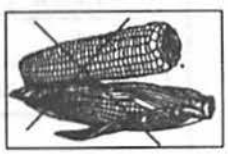



E. **Requirements:** 1.5 mg/day.

## IV. *Niacin (nicotinic acid, $B_3$):*

A. **Sources:**

1. Whole grain cereals.
2. Milk, meat, liver, and yeast.
3. Niacin can be synthesized endogenously from the amino acid **tryptophan:**
   *a)* Each 60 mg tryptophan can be converted to 1 mg niacin. This conversion requires vitamin $B_6$, as a coenzyme.

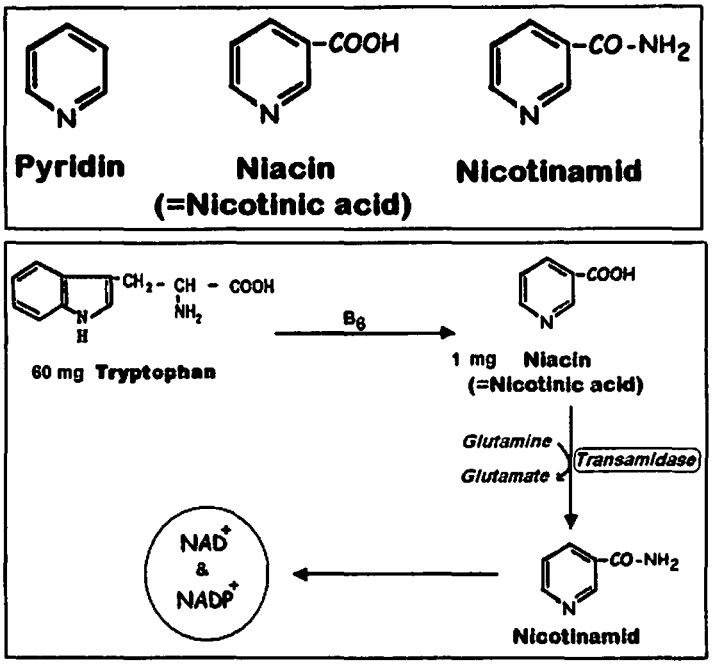


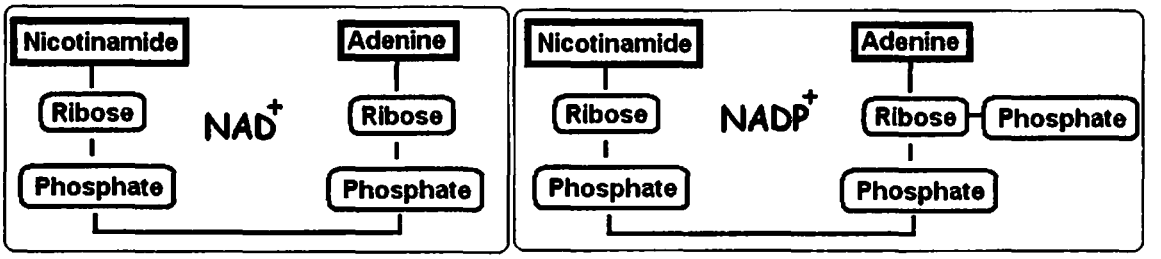
*b)* Meat is rich in tryptophan, so it is important source of niacin.

*c)* Corn is poor in both niacin and tryptophan.

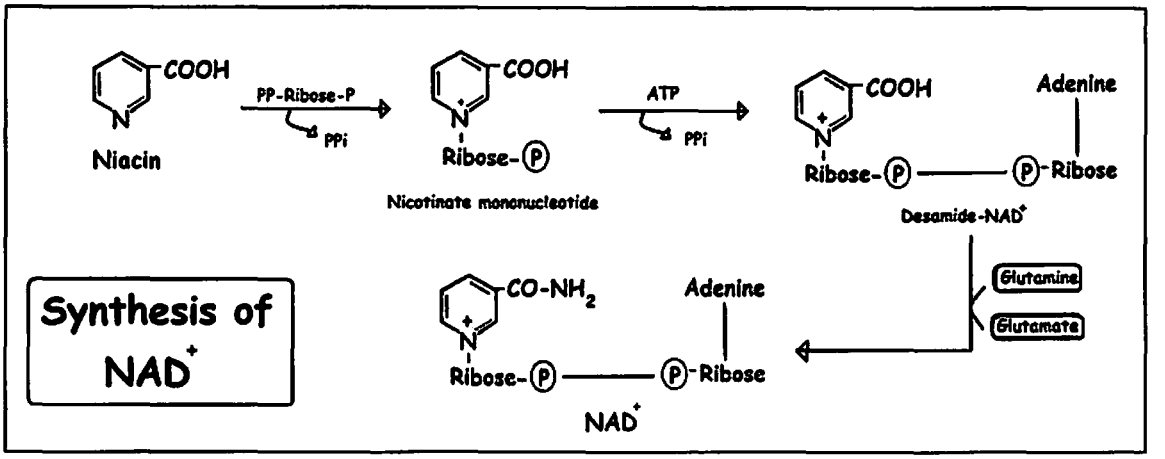
**B. Structure:**

1. Niacin (= nicotinic acid) is a pyridine derivative.
2. It is a nontoxic substance present in a toxic alkaloid nicotin of tobacco.
3. Active forms:
   *a)* Niacin is converted to the active form **nicotinamide** that enters in the structure of nicotinamide adenine dinucleotide ($NAD^+$) and nicotinamide adenine dinucleotide phosphate ($NADP^+$).
   *b)* Nicotiamide, a derivative of nicotinic acid contains **amide group**.

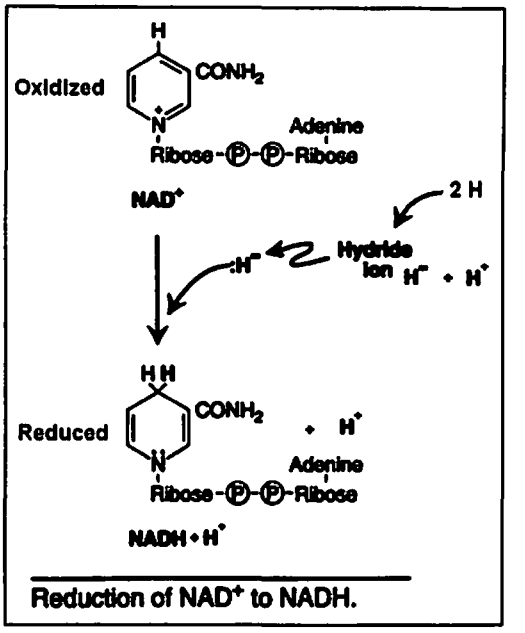



**C. Synthesis of $NAD^+$ and $NADP^+$:**



1. The formation of $NAD^+$ and $NADP^+$ occurs in the cytosol of liver cells. $NADP^+$ has similar structure in addition to phosphate.
2. $NAD^+$ and $NADP^+$ are present in two forms oxidized and reduced. They undergo reduction of pyridine ring by accepting a Hydride ion (hydrogen atom plus one electron).

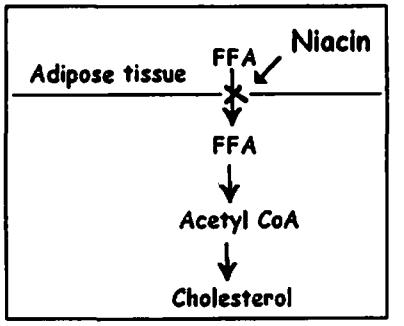


Reduction of $NAD^+$ to NADH.

## D. Functions of niacin:

1. **Formation of ($NAD^+$) and ($NADP^+$):** Niacin is essential for the formation of the coenzymes nicotinamide adenine dinucleotide ($NAD^+$) and nicotinamide adenine dinucleotide phosphate ($NADP^+$).
   *a)* These two coenzymes function as hydrogen carriers and they are essential for many biochemical oxidation-reduction reactions. These reactions are important in carbohydrate, protein and lipid metabolism.

2. **Lowering plasma cholesterol:** Niacin lowers plasma cholesterol concentration. This is due to inhibition of flow of free fatty acids (FFA) from adipose tissue which provides acetyl CoA molecules essential for cholesterol and triacylglycerols synthesis.



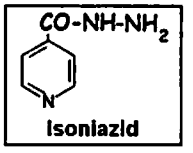

3. **Formation of ADP-ribose:** $NAD^+$ is a source of ADP-ribose: It is important for:
   *a)* ADP-ribosylation of protein.
   *b)* Poly ADP ribosylation of nucleoproteins involved in DNA repair mechanism.

**Summary of niacin functions:**
- Formation of NAD and NADP → Hydrogen carrier.
- Lowering plasma cholesterol.
- Formation of ADP-ribose for ribosylation of protein and DNA.

**E. Deficiency: → *Pellagra***

Deficiency of niacin causes pellagra, a disease affects the skin, GIT and central nervous system.

1. **Manifestations of pellagra:**
   Pellagra is called a disease of (4 $D_S$): diarrhoea, dermatistis, dementia and if not treated death.
2. **Causes:**
   *a)* Deficiency of niacin, tryptophan or vitamin $B_6$.
   *b)* Corn is deficient in both niacin and tryptophan. Thus people who depend on corn as a major source of protein as some farmers develop pellagra.
   *c)* **Hartnup's disease:** It is a hereditary disease in which there is defect in tryptophan absorption from intestine and tryptophan re-absorption by renal tubules → pellagra .
   *d)* **Argentaffinoma (malignant carcinoid syndrome):** In which large quantities of tryptophan is converted to serotonin. This occurs on the expense of niacin synthesis → pellagra.
   *e)* **Isoniazid:** It is a drug that is used in treatment of tuberculosis. Isoniazid binds with B6 → Excretion by kidney → pellagra.



Isoniazid

**Requirements:** Niacin 20 mg / day.

**F. Hypervitaminosis of niacin:**

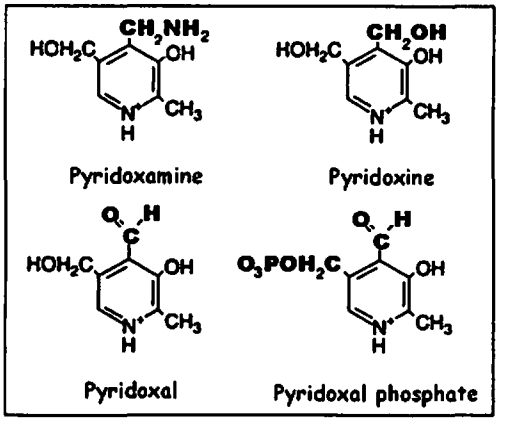
Intake of either nicotinic acid or nicotinamide in high doses (more than 500 mg/day) may cause liver damage.

## V. *Pyridoxine "vitamin $B_6$"*

**A. Sources:** Wheat, corn, egg yolk, liver and meat.

**B. Structure:**

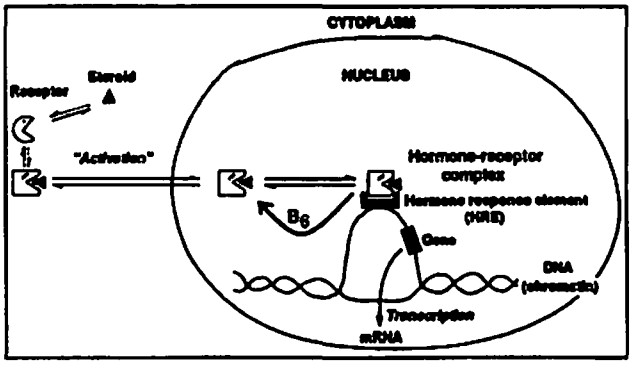
1. Vitamin $B_6$ include a group of vitamers derived from pyridine ring.
2. These are pyridoxine, pyridoxal and pyridoxamine.
   *a)* They differ in the nature of functional group attached to the ring.
   *b)* All 3 compounds can act as a precursors of the biologically active coenzyme pyridoxal phosphate



## C. Functions:

In the body, pyridoxine is converted to pyridoxal phosphate, which acts as a coenzyme for a large number of enzymes:

1. **In protein metabolism:** It acts as a coenzyme for amino acids metabolism in the following reactions:
   - *a)* **Transamination e.g.**
     Glutamate + Oxaloacetate ⇆ α Ketoglutarate + Aspartate
   - *b)* **Trans-sulfuration e.g.**
     **Methionine → Homocysteine (+ serine) → Cysteine + Homoserine**
   - *c)* **Deamination e.g.**
     Serine → Pyruvate + $NH_3$
   - *d)* **Decarboxylation e.g.**
     Glutamate . → GABA + $CO_2$
   - *e)* **SYNTHESIS OF:**
     1) **Heme synthesis e.g.**
     Glycine + Succinyl CoA → δ Aminolevulinic acid → Heme
     2) **vitamin $B_3$ (niacin) synthesis.**
     3) **Sphingosine synthesis:** Serine + Palmitate
   - *f)* **It takes a role in amino acids absorption from the intestine.**
2. **In carbohydrate metabolism:** Pyridoxal phosphate acts as a coenzyme of glycogen phosphorylase →
   Glycogen breakdown into glucose (glycogenolysis).




3. **In lipids metabolism:** Pyridoxal phosphate is important in steroid hormone action, where it removes the hormone- receptor complex from DNA binding, terminating the action of hormone.

## D. Deficiency:

1. **Pellagra** may result, because pyridoxal phosphate is needed for the conversion of tryptophan to niacin.
2. **Convulsions in young infants** due to deficient formation of GABA (inhibitory transmitter in brain).
3. **Anemia** (microcytic and hypochromic) due to deficient formation of heme and hemoglobin.
4. Disturbance in amino acids metabolism. This leads to growth

retardation and may be mental retardation.

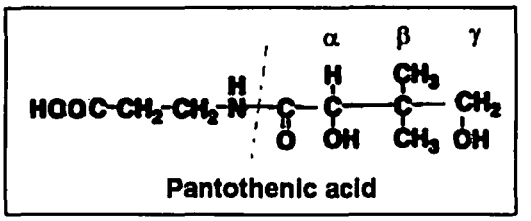
5. **Cancer breast, uterus and prostate:** due to defective action of B6 on steroid – DNA binding.
6. **Homocysteinuria:** It is due to inability to convert Methionine to cysteine.

E. **Hypervitaminosis of $B_6$:**

Intake of more than 200 mg/day $B_6$ may cause neurological damage.

F. **Requirements:** 2 mg / day.

## VI. *Pantothenic acid*

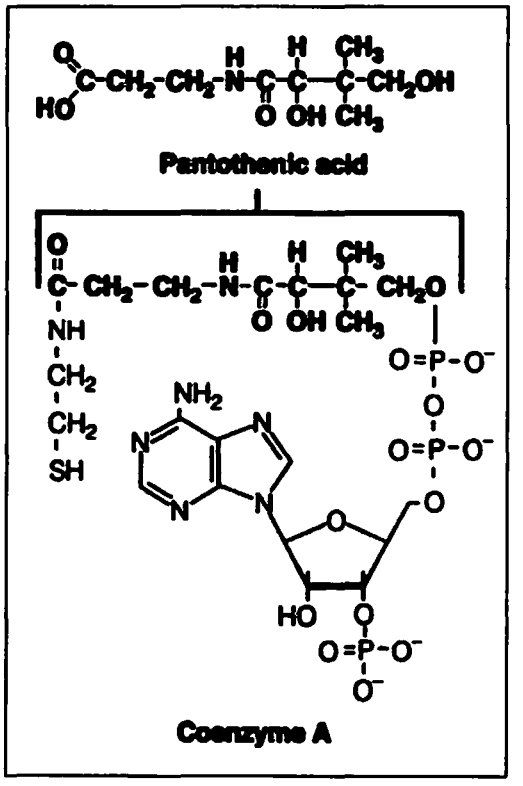



A. **Sources:**

1. Animal tissue as meat, liver, kidney.
2. Legumes.

B. **Structure:**

Pantothenic acid is formed of pantoic acid (α and γ dihydroxy β dimethyl butyric acid) connected to β-alanine.



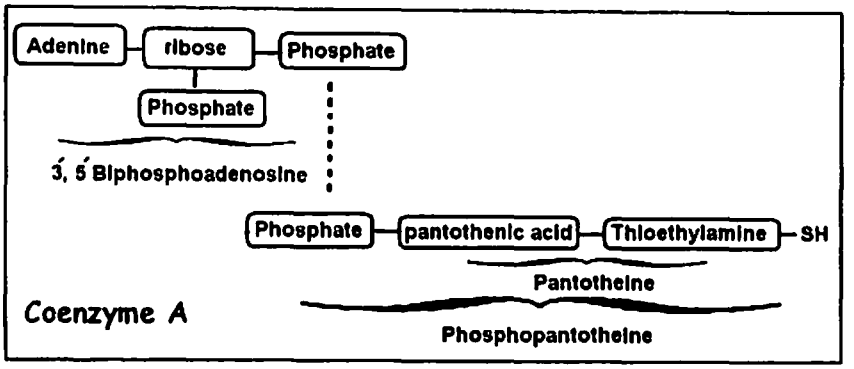

C. **Functions:**

Pantothenic acid enters in the structure of coenzyme A (CoA) and acyl carrier protein:

1. **Coenzyme A (CoASH):**
   - *a)* **Structure:** is formed of phosphpantothein (= phosphate + pantothenic acid + thioethylamine) attached to biphosphoadenosine.
   - *b)* **Function:**

     Coenzyme A acts in the transfer of acyl groups e.g. acetyl CoA, succinyl CoA, malonyl CoA and other carboxylic acids.

     1) **Acetyl CoA:** It is an important intermediate in metabolism of carbohydrate, lipids and protein metabolism.
     2) **Succinyl CoA:** used in heme synthesis and other reactions.
     3) **malonyl CoA:** is used in fatty acid synthesis.

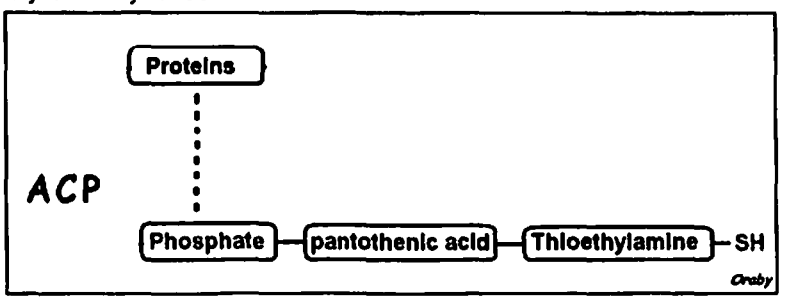



2. **Acyl carrier protein (ACP):**

   *a)* **Structure:** ACP is formed of: Pantothenic acid connected to phosphate and protein in one side and thioethyl amine in the other side.

   *b)* **Functions:**

   ACP is a component of fatty acid synthase enzyme required for fatty acid synthesis.




D. **Deficiency:** Deficiency of pantothenic acid causes no effect in human.

E. **Requirements:** 5 - 10 mg / day.

## VII. *Biotin*

A. **Sources:**

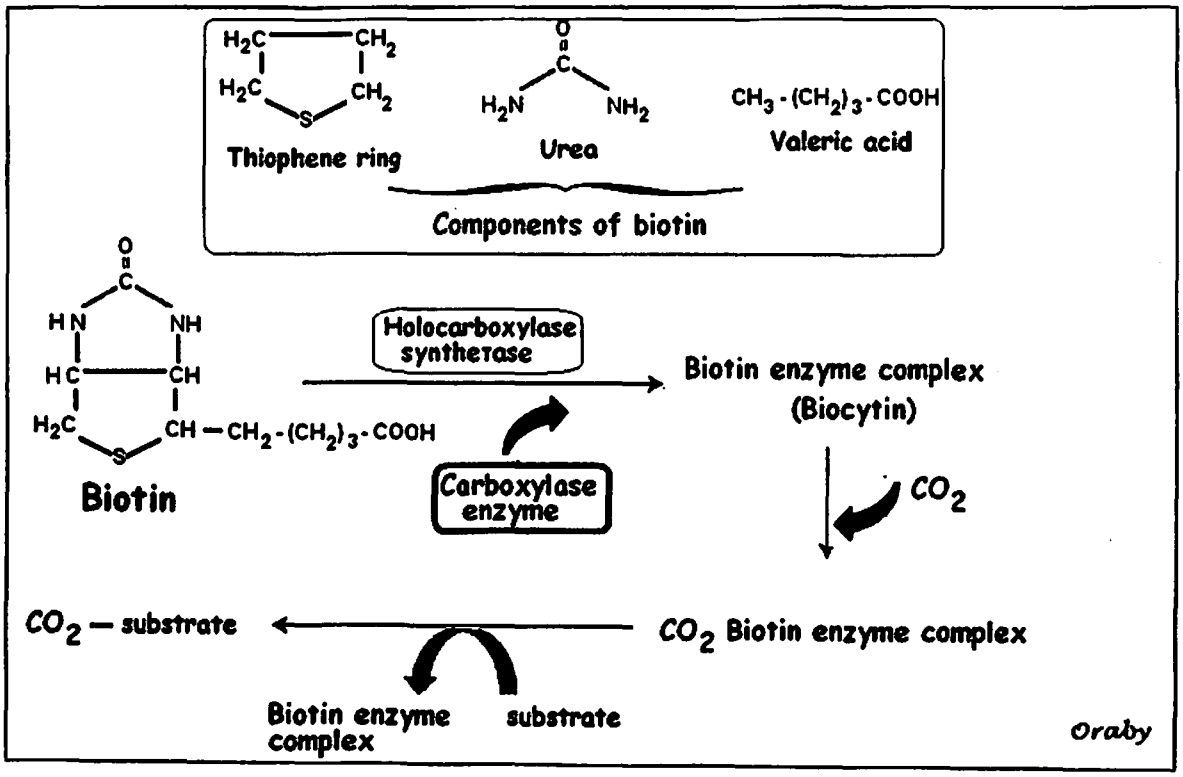
1. The intestinal bacteria synthesize most of the human requirements of biotin.
2. Egg yolk, animal tissues, tomatoes and yeast are excellent sources..

B. **Absorption:** In the ileum.

C. **Structure:**

1. Biotin consists of thiophene ring connected to urea with valeric acid as side chain.
2. Biotin acts as $CO_2$ carrier. It attaches to carboxylase enzyme to form **biocytin** a reaction catalyzed by holocarboxylase synthetase enzyme. Deficiency of such enzyme may lead to deficiency manifestation of biotin.

3. $CO_2$ is attached to biotin to form $CO_2$ biotin enzyme complex. The $CO_2$ group is then transferred to the substrate for carboxylation.




**D. Functions: → $CO_2$ fixation**

*a)* Biotin is a $CO_2$ carrier. It acts as coenzyme for carboxylase enzymes that catalyze carboxylation reactions ($CO_2$ fixation).

*b)* Example of important carboxylation reactions are:

1) **Carboxylation of acetyl CoA to malonyl CoA:** is important reaction in fatty acid synthesis.

2) **Carboxylation of pyruvate to oxaloacetate:** is important reaction in Gluconeogenesis i.e. synthesis of glucose from non-carbohydrate sources..

3) **Carboxylation of propinyl CoA** to give succinyl CoA.

2. **Regulation of cell cycle:** Biotin also has a role in regulation of cell cycle.

**E. Deficiency:**

1. **Deficiency of biotin does not occur in man because:**

*a)* The intestinal bacteria supply all the human needs.

*b)* Biotin is widely distributed in food.

2. **Biotin deficiency may result from:**
   *a)* **Ingestion avidin:** it is a glycoprotein present in uncooked egg white. It tightly binds biotin and prevents its absorption from the intestine.
   *b)* Deficiency of holocarboxydase synthetase enzyme in children. This enzyme is responsible for the attachment of biotin to carboxylase enzyme.
3. **The manifestations** of biotin deficiency include: muscle pain, dermatitis, glossitis, loss of appetite and nausea.

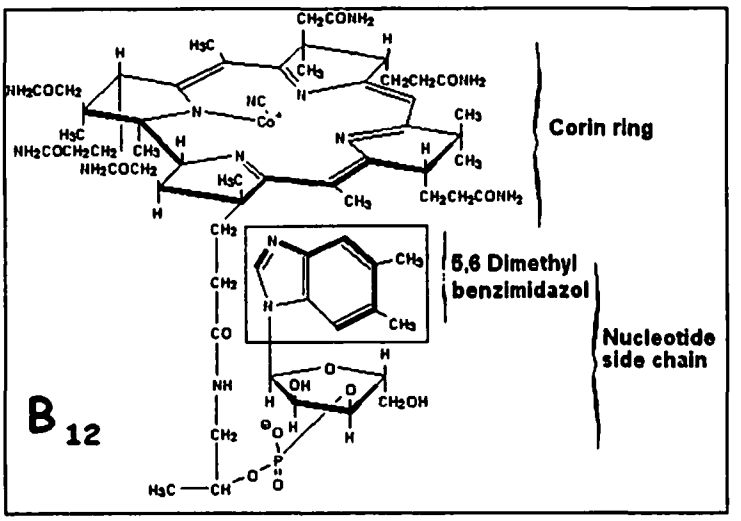
## VIII. *Vitamin $B_{12}$ = Cobalamins*

### A. Sources:

1. Meat, egg, milk and milk products.
2. Vitamin $B_{12}$ is **not present in plant sources**. This means that strict vegetarians (vegans) are at risk of developing $B_{12}$ deficiency.
3. Intestinal microorganisms synthesize $B_{12}$ in human colon, but it is not absorbed through the mucosa in this region of the gastrointestinal tract.

### B. Structure: Vitamin $B_{12}$ or cobalamin consists of:

1. A corin ring [formed of 4 pyrrole rings connected by methenyl groups (=CH-)].
2. Cobalt ion at in the center of corin ring. The cobalt is red in color. This is the cause of the red color of vitamin $B_{12}$.
3. A nucleotide side chain.



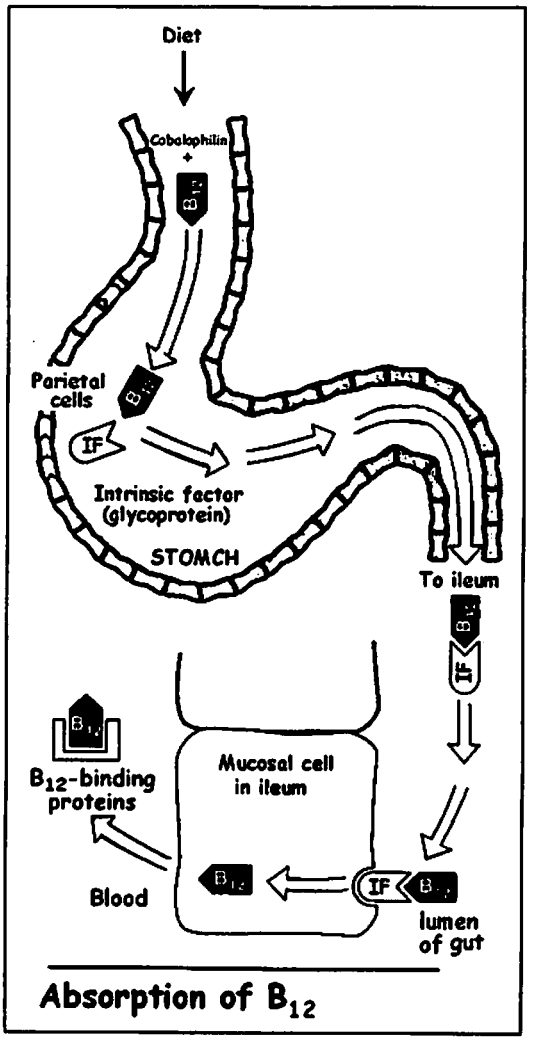
4. A cyano group (CN) attached to cobalt ion forming cyanocobalamin.
   **The cyano group may be replaced by either:**
   *a)* Hydroxy group (OH) → hydroxy cobalamin
   *b)* Methyl group ($CH_3$) → methylcobalamin.
   *c)* 5 Hydroxyadenosine → adenosyl-cobalamin.
   Note: The cyanocobalamine is the most stable form.

## C. Storage of $B_{12}$:

1. The liver stores 50% to 90% of body's $B_{12}$.
2. This reserve can supply the body with $B_{12}$ for 1-2 years even in complete absence of vitamin intake.

## D. Absorption and transport in blood:

1. In the mouth $B_{12}$ binds to a protein called cobalophilin. This protein is secreted in the saliva.
2. In the duodenum, cobalophilin is hydrolyzed, releasing the vitamin for binding to intrinsic factor (IF) to form IF- $B_{12}$ complex. Intrinsic factor (IF) is a glycoprotein secreted by the gastric parietal cells
3. Then IF- $B_{12}$ complex binds with specific ileal receptor. A pH above 6 and calcium ions are required to promote vitamin absorption.
4. Vitamin $B_{12}$ passes via portal circulation to the liver to the general circulation.
5. Vitamin $B_{12}$ is carried in the plasma by a number of carrier globulins, named transcobalamin II, transcobalamin I and R proteins. They transport $B_{12}$ to the tissues. It binds to specific cell surface receptor to enter the cell.



Absorption of $B_{12}$

## E. Physiological functions:

Vitamin $B_{12}$ is required in humans for synthesis of methionine. Tetrahydrofolate, and myelin sheath:

1. Synthesis of Methionine.
2. Synthesis of tetrahydrofolate (FH4).
3. Formation of myelin sheath.

### 1. Methionine:

*a)* **Synthesis:**

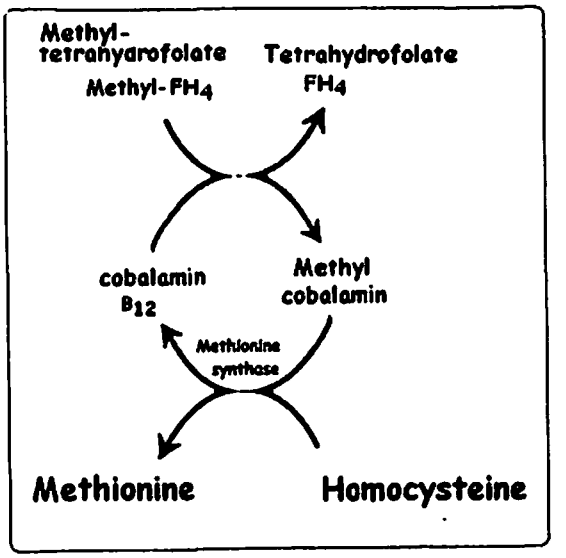
1) Vitamin $B_{12}$ (in the form of methylcobalamin) acts as coenzyme for methionine synthase enzyme.

2) This enzyme catalyzes the conversion of homocysteine into methionine.

*b)* **Functions:** It is important for:-

1) Synthesis of phospholipids. The later enters in the structure of myelin sheath.

2) Prevention of fatty liver.



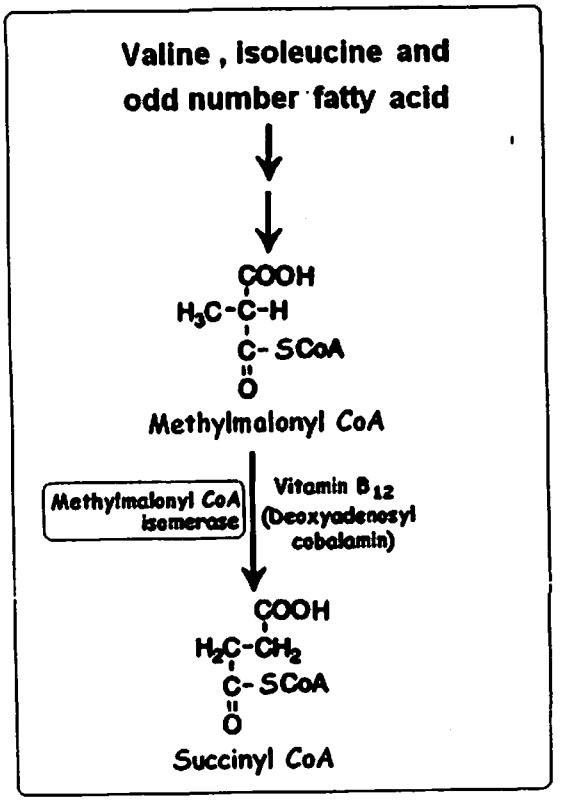

### 2. Tetrahydrofolate:

*a)* **Synthesis:**

1) Methyl-tetrahydrofolate (methyl-FH4) is converted into Tetrahydrofolate (FH4) by transferring methyl group ($-C_{H3}$) to cobalamin. Then methylcobalamin transfers the ($-C_{H3}$) to homocysteine to form methionine.

*b)* **Functions:**

1) (FH4) is required for cell division e.g. hemopoiesis.




**Reactions requiring cofactor forms of vitamin $B_{12}$**

### 3. Isomerization of L-methyl malonyl CoA to succinyl CoA:

*a)* Methyl malonyl CoA is formed in the mitochondria in the course of

catabolism of valine and isoleucine amino acids. It also formed as a result of oxidation of odd number fatty acids.

*b)* Vitamin $B_{12}$ (deoxyadenosylcobalamin) acts as coenzyme for methyl malonyl CoA isomerase enzyme that catalyzes the conversion of methylmalonyl CoA into succinyl CoA.

## F. Deficiency:

### 1. It occurs in the following conditions:

*a)* Decrease vitamin $B_{12}$ intake. This may occur among vegetarians. I.e. people who eat vegetables only.

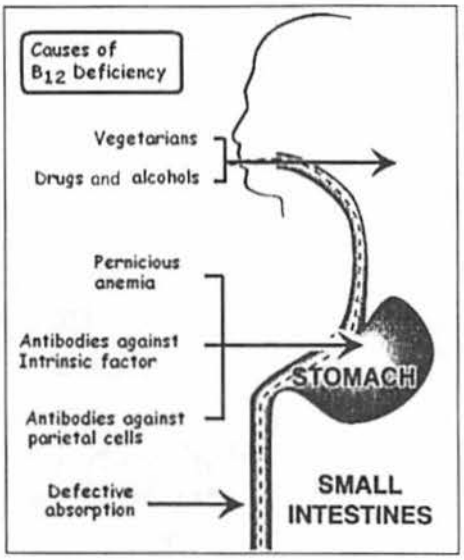
*b)* Drugs induced vitamin $B_{12}$ deficiency as neomycin antibiotic and alcohol.

*c)* Atrophy of gastric mucosa → due to lack of intrinsic factor → **pernicious anemia** (PA).

*d)* Antibodies against gastric parietal cells.

*e)* Antibodies against intrinsic factors.

*f)* Defective absorption as in sprue or regional enteritis.




### 2. Manifestations of vitamin $B_{12}$ deficiency:

*a)* **Megaloblastic anemia:**

1) It is a macrocytic hyperchromic anemia.
2) It is due to abnormal replication of DNA in hematopoietic tissue.
3) It is due to direct insufficiency of folate or indirectly to a cobalamin insufficiency.

*b)* **Neurological manifestations:**

1) It is due to the lack of myelin sheath formation due to the deficiency of methionine and disturbance in the metabolism of odd number fatty acids.
2) **It includes:-**
   - **i-** Subacute combined degeneration of the spinal cord where both motor and sensory tracts are affected.
   - **ii-** Peripheral neuritis leads to numbness, tingling and weakness of extremities.

   **Note:** Administration of folic acid to PA patient improves the blood picture but aggravates nervous system lesion.

**G. Laboratory findings:**

1. Increased the excretion of methylmalonyl CoA in urine (= methylmalonyl aciduria).
2. Increased the excretion of Homocysteine (=Homocysteinuria).

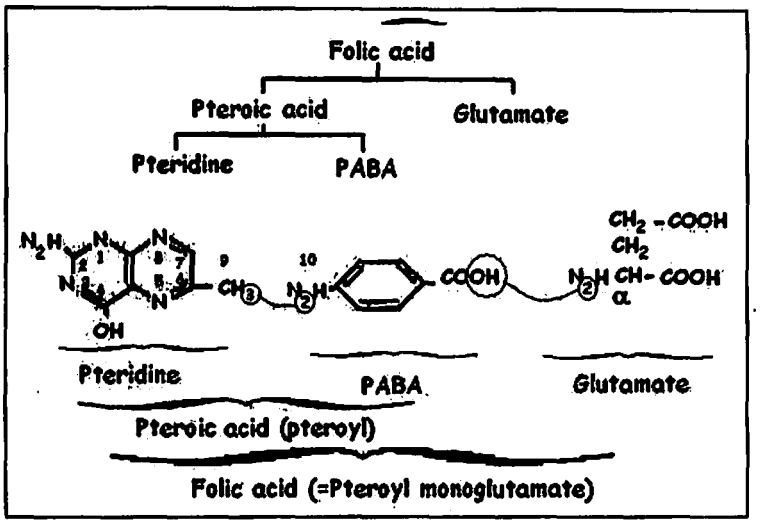
**H. Requirements:** 4 ug / day.

## IX. *Folic acid (= folate = folacin)*

**A. Sources:**

1. The major source is leafy vegetables.
2. Liver, beans and whole grain cereals.

**B. Structure:**



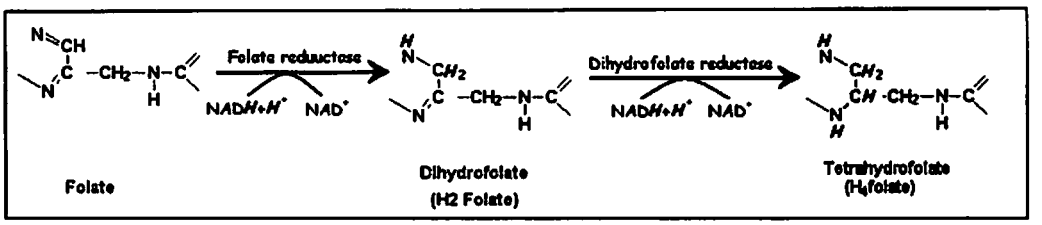

1. Folic acid is formed of pteroic acid conjugated to one or more glutamic acid residues.
   *a)* Pteroic acid consists of pteridine ring (2 amino, 4 hydroxy, 6 methyl pteridine) connected to para-aminobenzoic acid (PABA).
   *b)* In plants, folic acid contains (2:7) glutamic acid residues, each attached to γ carbon of glutamate.

**C. Absorption:**

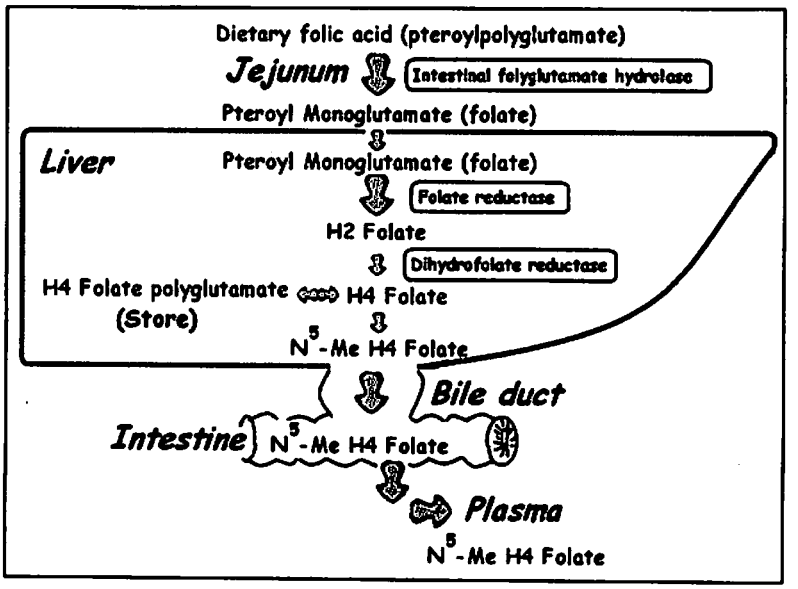
1. In the jejunum, the pteroylpolyglutamate is broken to pteroylmonoglutamate by the intestinal folypolyglutamate hydrolase.

   ***Pteroylpolyglutamate → Pteroylmonoglutamate***

2. Pteroylmonoglutamate is the absorbable form of folate.
3. Then folate enters the liver through the portal circulation. The liver converts folate into dihydrofolate ($H_2$ folate) and tetrahydrofolate ($H_4$ folate) as follows:




4. The liver converts some of tetrahydrofolate monoglutamate to tetrahydrofolate polyglutamate which is then stored.
5. Another fraction of folate is excreted in the bile as $N^5$-methyl tetrahydrofolate ($MeH_4$ folate) which is reabsorbed and it is the major circulating form of folate.




## D. Functions of folic acid:

1. The active form is tetrahydrofolic acid ($H_4$ folate) which functions as a carrier for one-carbon groups.
2. ***The one carbon groups are utilized for the synthesis of:***
   - *a)* Synthesis of DNA and RNA through synthesis of purines (adenine and guanine) and methylation of uracil into thymine. Thus folate is required for cell formation including blood cells.
   - *b)* Synthesis of nonessential amino acids e.g. serine and glycine.
   - *c)* Conversion of homocysteine into methionine

NOTE:

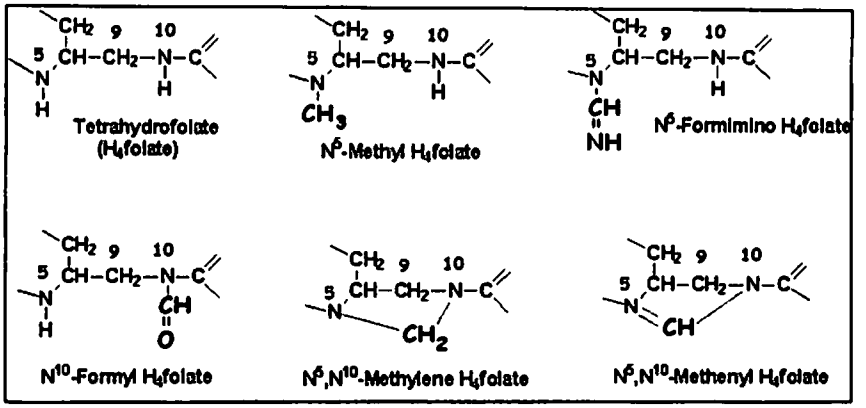
- **The one-carbon groups carried by $H_4$ folate may be: Methyl ($-CH_3$), mythylene ($-CH_2$), formyl (-CHO) or formiamino group (CH=NH).**
- **All one-carbon groups are inter-convertible:-**

  **e.g. (-CHO) ⇆ ($-CH_2OH$) ⇆ (-CHO)**
- **The one-carbon group may be carried on $N^5$ or $N^{10}$ or both of $H_4$ folate.**

## E. Sources of one carbon groups:

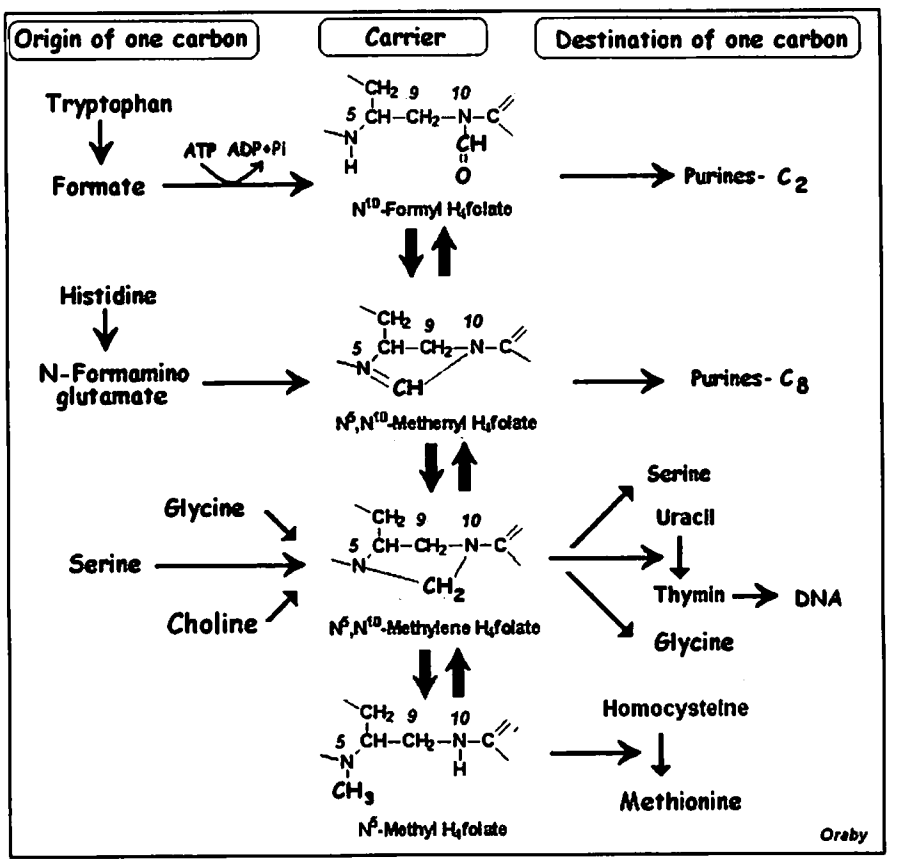
1. **β Carbon of serine is the major source of the one carbon group for the $H_4$ folate.**

2. Tryptophan
3. Histidine.




## F. Fate (and functions) of one carbon groups:

1. Synthesis of glycine (see glycine metabolism).
2. Conversion of glycine to serine (see serine metabolism).
3. Conversion of uracil to form thymine (dUMP to dTMP). Thymine is important for DNA synthesis.
4. Conversion of homocysteine to methionine.
5. Provides C2 and C8 purines.

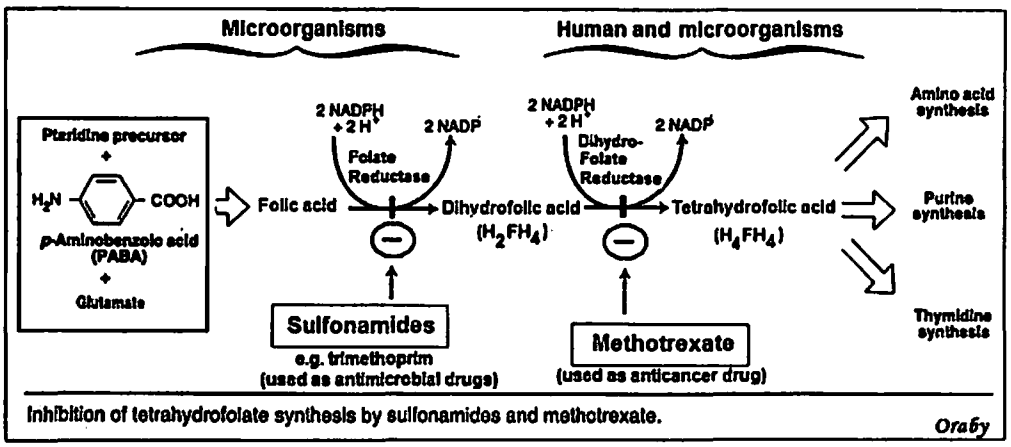


## G. Deficiency:

1. The manifestations are due to defective synthesis of DNA and RNA → defective cell formation including blood cells.
2. ***The manifestations of folate deficiency include:***
   *a)* **Pancytopenia:** i.e. all blood cells are affected.
      1) Megaloblastic anemia: (macrocytic anemia).
      2) Leucopenia: ↓ W.B.Cs.
      3) Thrombocytopenia: ↓ Platelets.
   *b)* **Impaired growth and neural tube defects in fetus.**

## H. *Drugs inhibit folic acid formation* (folate antagonists):

1. ***Trimethoprim:*** **(antibiotic)**
   *a)* It is a drug containing sulfonamide.
   *b)* It is a selective inhibitor of folate reductase in bacteria (gram negative bacteria) and has a little effect on human.
2. ***Methotrexate:*** **(anticancer)**
   *a)* Is a drug that binds more strongly to dihydrofolate reductase. It has effect on both human and microorganisms.
   *b)* It is used as anticancer.



Inhibition of tetrahydrofolate synthesis by sulfonamides and methotrexate. *Orafy*

## I. Requirements:

1. 200 ug / day.
2. The requirements increase during late pregnancy and lactation..

***Summary of functions and deficiency manifestations of vitamins:***

| Vitamin | | Functions | Deficiency |
|---|---|---|---|
| A | Retinoids | 1- Night vision.<br>2- Reproduction.<br>3- Normal growth.<br>4- Maintenance of epithelial cells.<br>5- Antioxidant.<br>6- Retinoic acid is important for synthesis of:<br>a. Glycoproteins.<br>b. Phospholipids.<br>c. Cell differentiation. | 1- Night blindness.<br>2- Xeroophthalmia.<br>3- Roughness of skin and mucus membranes. |
| D | Calcitriol | 1- Maintains plasma calcium.<br>2- Mineralization of bones.<br>3- Synthesis of osteocalcin. | 1- In children: Rickets.<br>2- In adults: osteomalacia. |
| K | | 1- Synthesis of clotting factors 1,2,7 ,9<br>2- Synthesis of osteocalcin. | Impaired blood clotting. |
| E | Tocopherols | Antioxidant, especially in cell membrane. | Rare |
| C | L-Ascorbic acid | 1- Hydroxylation of of proline and lysine in collagen synthesis.<br>2- Antioxidant.<br>3- Absorption of iron. | Scurvy<br>•Defective collagen ↓ bone and teeth synthesis.<br>•Bleeding into gum and muscles.<br>•Defective iron absorption. |
| B1 | Thiamin | 1. Oxidative decarboxylation of α-ketoacids:<br>2. Transketolation reactions:<br>3. nerve conduction and structure of nerve membrane. | Beriberi<br>•Dry beriberi<br>o Peripheral neuritis<br>o Muscle wasting<br>•Wet beriberi<br>o Heart failure<br>o edema |
| B2 | Riboflavin | Synthesis of FMN and FAD. Both acts as hydrogen carriers. | Ocular disturbances, cheilosos, glossitis and dermatitis |
| B3 | Niacin<br>(nicotinic acid) | 1. Formation of ($NAD^+$) and ($NADP^+$): These two coenzymes function as hydrogen carriers.<br>2. Lowering plasma cholesterol:<br>3. Formation of ADP-ribose. | Pellagra (3 Ds):<br>1- Dermatitis.<br>2- Dementia.<br>3- Diarrhea. |
| B6 | Pyridoxine | Coenzyme in transamination and decarboxylation of amino acids and glycogen phosphorylase. It has a role in steroid hormone action. | Disturbance of amino acids metabolism e.g. convulsions. |
| | Pantothenic acid | Enter in the structure of CoA and ACP. | |
| | Biotin | Coenzyme in carboxylation reactions. | Rare because it is synthesized by intestinal bacteria. |
| B12 | Cobalamin | 3. Synthesis of methionine.<br>4. Conversion of methyl-FH4 into FH4<br>5. Isomerization of methyl-malonyl CoA. | 1- Pernicious anemia.<br>2- Neurological disorders |
| | Folic acid | Transfer of one carbon fragments. | Megaloblastic anemia |

# Chapter 7 *Digestion, Absorption, Fermentation and Putrefaction*

## I. *Definition:*

Digestion is the breakdown of foodstuff into the simplest forms to be easily absorbed.

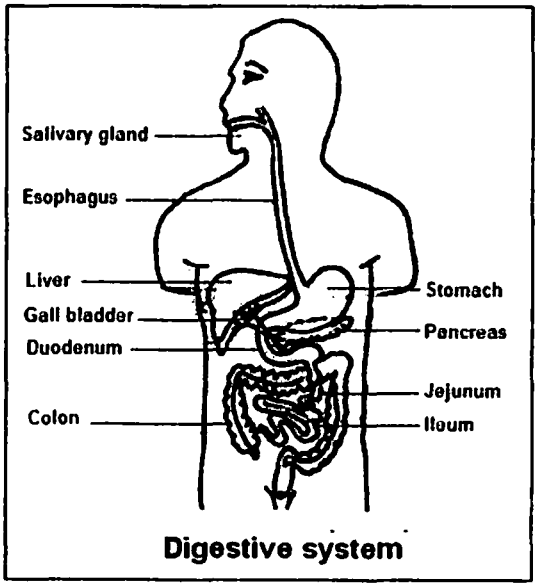
**A.** The simplest forms of carbohydrates are monosaccharides.

**B.** The simplest forms of proteins are amino acids.

**C.** The simplest forms of lipids are fatty acids and glycerol.

## II. *Structure of digestive system:*

The digestive system includes: Salivary glands, esophagus, stomach, duodenum, small intestine (Jejunum, ileum), colon, rectum, liver, gall bladder and pancreas.



Digestive system

## III. *Digestion of carbohydrate*

The chief carbohydrates of food are: starch, sucrose, lactose and cellulose.

**A.** **<u>Starch:</u>**

Starch is digested by the salivary amylase, pancreatic amylase and intestinal maltase.

**1. Salivary amylase:**

*a)* Optimum pH: 6.7 and activated by chloride ions.

*b)* The salivary amylase hydrolyzes cooked starch into dextrins and maltose.

***Starch → Amylodextrin → Erythrodextrin → Achrodextrin → Maltose.***

**2. Pancreatic amylase:**

*a)* Optimum pH: 7.1 and activated by chloride ions.

*b)* The pancreatic amylase hydrolyzes the cooked and uncooked starch into dextrins then into maltose.

**B. Digestion of disaccharides:**

**1. Maltose:**

Maltose is digested by intestinal ***maltase***. Optimum pH: 6. It hydrolyzes maltose into 2 molecules of glucose.

***Maltose → Glucose + Glucose***

**2. Sucrose:**

Sucrose is digested by the intestinal ***sucrase***. Optimum pH: 6. It hydrolyzes sucrose into glucose and fructose.

***Sucrose → Glucose + Fructose***

**3. Lactose:**

*a)* Lactose is digested by the intestinal ***lactase*** enzyme (optimum pH:6). It hydrolyzes lactose into glucose and galactose.

***Lactose → Glucose + Galactose***

*b)* **Lactase enzyme deficiency:**

1) Deficiency of lactase → No digestion of lactose.

2) So, lactose remains in the intestine. This leads to:-

i- Increase of the osmotic pressure inside the intestine → ↑ water content in the intestine → diarrhea and dehydration.

ii- Fermentation of lactose due to the action of intestinal bacteria on it → production of $CO_2$ gas → distension of abdomen and abdominal cramps.

**C. Cellulose:**

1. Cellulose is not digested because there is no enzyme in the gastrointestinal tract in man that can digest the β 1,4 linkage of cellulose.
2. **Importance of cellulose in food:**
   The undigested cellulose increases the volume of stool. This stimulates the intestinal motility and prevents constipation.

**IV. *Absorption of carbohydrate:*** see carbohydrate metabolism, part II.

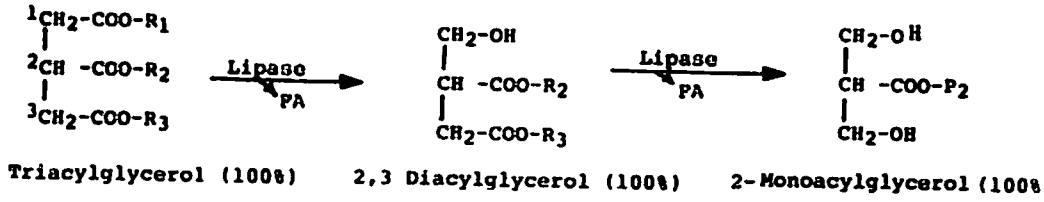
**V. *Digestion of lipids*** (triacylglycerols, cholesterol and phospholipids):

**A. *triacylglycerols digestion:***

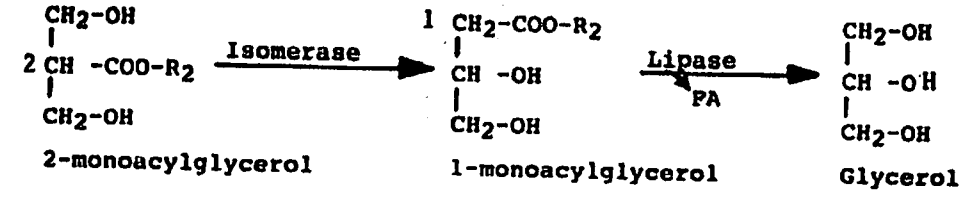
1. Triacylglycerols are first emulsified and then undergo enzymatic hydrolysis, by lipase enzymes.
   *a)* Emulsification (i.e. breakdown of large fat globules into small ones) is done mainly by bile salts in small intestine.

*b)* Lipase enzymes are gastric, pancreatic and intestinal lipases. The most active is the pancreatic lipase. They are secreted in the form of inactive enzymes.

2. **Inactive pancreatic lipase is activated in the duodenum by:**
   *a)* **Bile salts:** which are produced by the liver. Bile salts also combine with digested lipids to form water soluble **micelles** (by decreasing surface tension). This helps **absorption** of lipids.
   *b)* **Co-lipase:** which is a protein produced by the pancreas.
   *c)* **calcium ions:** $Ca^{2+}$.
3. **Action of pancreatic lipase: (pH:8):**




*a)* The 72% of 2-monoacylglycerol molecules undergo no further digestion. 28% of 2-monoacylglycerol molecules are digested to glycerol and fatty acids as follows:




*b)* Thus the end products of digestion of triacylglycerols are:
   1) 72%: 2-monoacylglycerol + fatty acids.
   2) 28%: Glycerol + fatty acids.
4. **Gastric lipase: (pH:7):**
   Gastric lipase may be of value in infants (pH: 5) acting on milk fat.

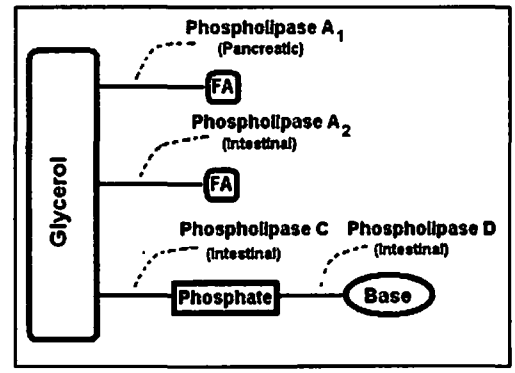
## B. Cholesterol digestion:

1. Cholesterol may be present as free or combined with FA (cholesterol ester).
2. Cholesterol itself undergoes no digestion.
3. Cholesterol esters are digested by cholesterol esterase enzyme. It hydrolyzes them into cholesterol and fatty acid.

## C. Phospholipids digestion:

1. Phospholipids are digested by phospholipase enzymes secreted from the pancreas and the intestine.
2. **Phospholipases are:** Phospholipase $A_1$, phospholipase $A_2$ (B), phospholipase C and phospholipase D.

3. **Phospholipases are activated by:**
   *a)* Bile salts and calcium ions.
   *b)* They act on phospholipids, hydrolyzing them into:
      1) Fatty acids.
      2) Glycerol.
      3) Phosphate.
      4) Nitrogenous base.




## VI. *Absorption of lipids: see lipids metabolism, part II.*

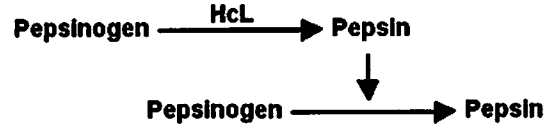
## VII. *Digestion of proteins*

### A. In the mouth:

No protein digestion.

### B. In the stomach:

1. **Pepsin:**
   *a)* pH: 1.2
   *b)* Pepsin is secreted in an inactive form called pepsinogen.
   *c)* Pepsinogen is first activated by gastric HCl into pepsin. Then pepsin itself activates pepsinogen (autoactivation).




   **d) Action of pepsin:**
      1) Pepsin is endopeptidase i.e. acts on the amino acids in the middle of polypeptide chains.
      2) It hydrolyzes the bonds formed by aromatic amino acids e.g. tyrosine.
      3) Pepsin releases large polypeptides and few free amino acids from dietary proteins.

2. **Rennin (optimum pH: 4):**
   *a)* It causes the coagulation of milk (milk clot).
   *b)* Rennin is important for infant because the formation of milk clot prevents the rapid passage of the milk from the stomach. This gives the baby the sense of fullness.
   *c)* **Action of rennin:**
      a) Rennin acts on casein, which is the main milk protein.
      b) In presence of calcium ions, rennin converts casein into insoluble calcium paracaseinate (milk clot).
      c) The digestion of calcium paracaseinate is completed by pepsin.

Casein $\xrightarrow{\text{Rennin}}$ Paracasein $\xrightarrow{Ca^{++}}$ Insoluble calcium paracaseinate (Milk clot)

C. **In the intestine:**

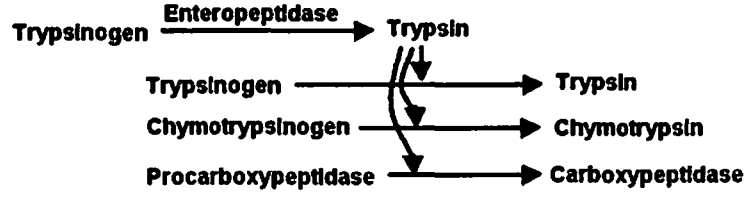
Two different organs, pancreas and intestine produce enzymes act on protein in the intestine.

1. **Pancreatic enzymes:** These include trypsin, chymotrypsin, carboxypeptidase, elastase and collagenase.

*a)* **Trypsin (optimum pH: 8):**

1) Trypsin is secreted as an inactive proenzyme: trypsinogen.

2) Trypsinogen is activated to trypsin at first by




enteropeptidase enzyme (produced by intestinal mucosa), then autocatalytically by other trypsin molecules that have already been activated by enteropeptidase enzyme.

3) **Action of trypsin :**

Trypsin is endopeptidase hydrolyzing the peptide bonds formed by basic amino acids e.g. lysine and arginine. It releases smaller peptides and more free amino acids.

4) Trypsin acts also as activator for all other inactive pancreatic enzymes.

*b)* **Chymotrypsin:**

1) Chymotrypsin is secreted as inactive proenzyme: chymotrypsinogen. It is activated by trypsin enzyme.

2) **Action of chymotrypsin :**

It is endopeptidase hydrolyzing the peptide bonds formed by aromatic amino acids (its action is similar to that of pepsin).

*c)* **Carboxypeptidase :**

1) It is secreted as an inactive proenzyme: procarboxypeptidase and activated by trypsin enzyme.

2) **Action of carboxypeptidase :**

i- It is exopeptidase i.e. acts on the periphery of polypeptide chains .

ii- Carboxypeptidase hydrolyzes the peptide bonds adjacent to the free -COOH group of the polypeptide chain, releasing each time a single free amino acid.

*d)* **Elastase :**

1) It is secreted as an inactive proenzyme: proelastase, and activated also by trypsin.
2) Action of elastase:
   i- It is endopeptidase.
   ii- In spite of its name, it hydrolyzes the peptide bonds formed by small amino acids e.g. alanine, glycine and serine.

*e)* **Collagenase:**

An enzyme catalyzes the hydrolysis of collagen.

2. **Intestinal enzymes: Aminopeptidase:**

It is an exopeptidase acting on the peptide bond at the free $-NH_2$ of the polypeptide chain liberating single amino acid at a time.

## VIII. *Hormones stimulating gastrointestinal secretion:*

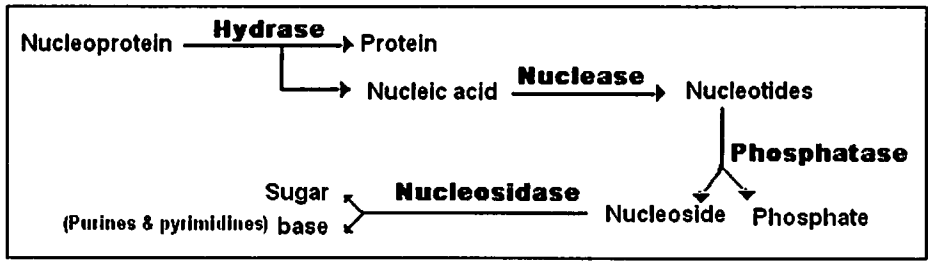
see protein metabolism, part III.

**IX.*Absorption of proteins:*** see protein metabolism, part III.

## X. *Digestion of nucleoproteins*

A. Nucleoproteins are digested by a group of enzymes produced by the intestinal mucosa:-

1. Hydrase, nuclease, phosphatase and nucleotidase.




# *Digestive juices*

## I. *Saliva*

A. There are 3 pairs of salivary glands: parotid, submixillary (submandibular) and sublingual.

B. **Physical properties of saliva:**

1. **Volume:** 1000 - 1500 ml / day.

2. **pH:** 6.7 (slightly acidic).
3. **Color:** Colorless.

C. **Composition:** The saliva consists of:

**Saliva**

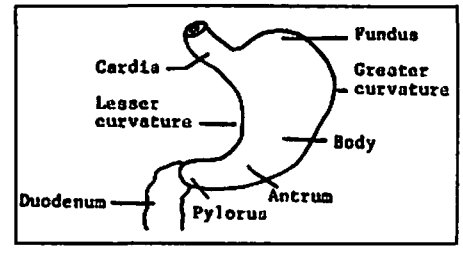
- **1% Solids**
  - **(2/3) Organic maters**
    - Salivary amylase, mucin and lysozyme enzyme.
    - Mucin (it gives the viscocity of saliva)
  - **(1/3) Inorganic maters**
    - $Ca^{2+}$, $K^{+}$, $Na^{+}$, $Mg^{2+}$
    - $SO_4^{2-}$ (sulfate), $PO_4^{3-}$ (phosphate)
    - $HCO_3^{-}$ (bicarbonate) and Cl (chloride)
- **99% water**

D. **Functions of saliva:**

1. It moistens the mouth and helps speech.
2. It moistens the food and helps swallowing.
3. It keeps the **mouth clean.**
4. **Digestion:** salivary amylase acts on cooked starch converting it into maltose (see digestion of carbohydrate).
5. **Antibacterial action:** Lysozyme is an enzyme that kills bacteria.
6. **Excretory action:** Mercury, lead and iodide may be excreted with saliva in the mouth.
7. **Buffering action:** Saliva contains phosphate buffers, which prevents the effect of acids on teeth.

## II. *Gastric juice*

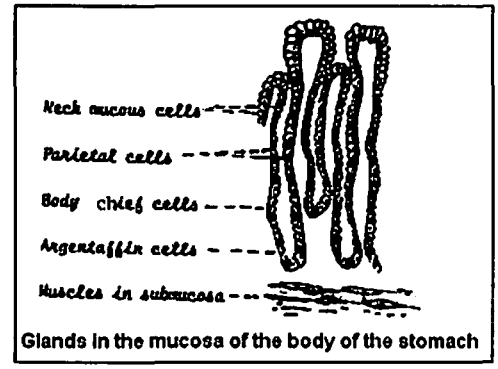
A. **Anatomy of the stomach:** See diagram.




B. **Types of gastric cells:**

The mucosa membrane of stomach contains 4 types of cells:-

1. **Body chief cells:** they secrete gastric enzymes.
2. **Parietal or oxyntic cells:** they secrete HCl.
3. **Mucosa cells:** they secrete mucus.
4. **Argentaffin cells:** of unknown function.



Glands in the mucosa of the body of the stomach

C. **Physical properties of gastric juice:**

1. **Volume:** 1000 ml / day.
2. **pH:** 1-2 (highly acidic due to the presence of HCl).

**D. Composition:**

**Gastric secretion**

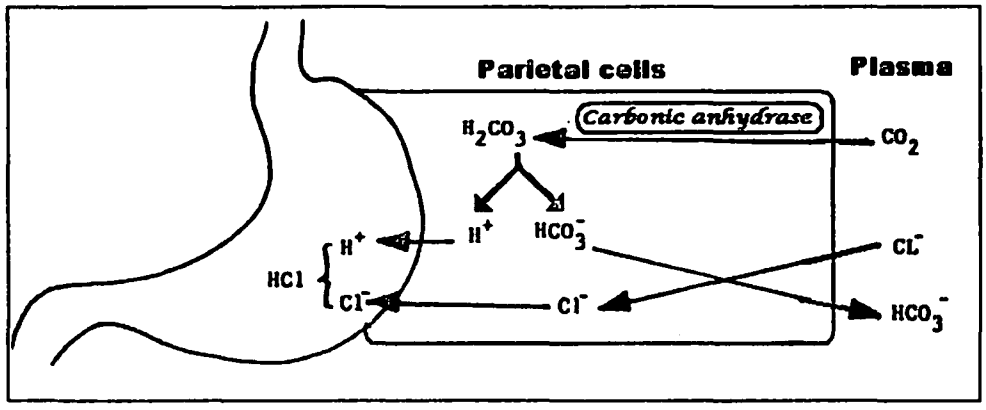
- **1% Solids**
  - **(2/3) Organic maters**
    - Enzymes: pepsin, rennin, lipase
    - Intrinsic factor
    - Mucin
  - **(1/3) Inorganic maters**
    - $Na^+$ , $K^+$ , $H^+$ , $CL^-$
- **99% water**

**E. Functions of gastric secretion:**

1. **Digestion:** Pepsin, rennin and lipase enzymes have digestive action (see protein and lipid metabolism).
2. **Intrinsic factor:** Is a glycoprotein essential for vitamin $B_{12}$ absorption.
3. **Mucin:** Covers the inner surface of gastric mucosa. Thus it protects the mucosa from proteolytic effect of gastric enzymes.
4. **HCl:** Has the following functions:
   *a)* It activates pepsinogen into pepsin and it gives an optimum pH for pepsin action.
   *b)* Antibactrial action: it kills bacteria and parasites.
   *c)* It helps iron and calcium absorption.
   *d)* It stimulates the secretion of secretin hormone from the duodenum.

**F. Mechanism of HCl formation:**

1. It is formed by parietal cells.
2. The mechanism is shown in diagram.
3. **Alkaline tide:** After meal, HCl formation increases. This leads to excess bicarbonate in blood which is excreted by the kidney in theurine. This leads to alkalinity of urine.



## III. *Intestinal juice: (Succus entericus)*

**A. Physical properties:**

1. **Volume:** 0.5 -1 liter / day.
2. **pH:** 7.8

**B. Composition:**

**Succus entericus**

- **2% Solids**
  - **Organic maters**
    - Mucin
    - Enzymes:
      - Disaccharidases: maltase, sucrase and lactase
      - Aminopeptidase
      - Intestinal lipase
      - Nucleotidases and nucleases
  - **Inorganic maters**
    $Ca^{2+}$, $Na^{+}$, $K^{+}$, $HCO_3^{-}$, $CL^{-}$, $PO_4^{3-}$
- **98% water**

**C. Functions:**

1. Digestion (see carbohydrate, protein and lipids digestion).

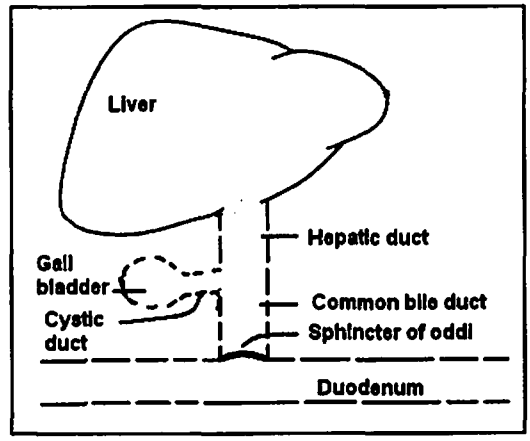
## IV. *Pancreatic juice*

**A. Volume:** 1 liter / day

**B. pH:** 8, it is the most alkaline juice in the body.

**C. Composition:**

1. **Inorganic substances:** $Ca^{2+}$ , $Na^{+}$ , $K^{+}$ , $HCO_3^{-}$, $Cl^{-}$ , $PO_4^{3-}$ ...etc.
   $HCO_3^{-}$content is the cause of alkalinity.
2. **Organic substances:**
   *a)* **Mucin.**
   *b)* **Enzymes:**
      1) Trypsin, chymotrypsin and carboxypeptidase for protein digestion.
      2) Ribonuclease and deoxyribonuclease for nucleic acids digestion.
      3) Pancreatic amylase for starch digestion.
      4) Pancreatic lipase for fat digestion.




## V. *Liver secretion (Bile):*

Bile is the secretion of liver cells, which passes into bile duct to the duodenum.

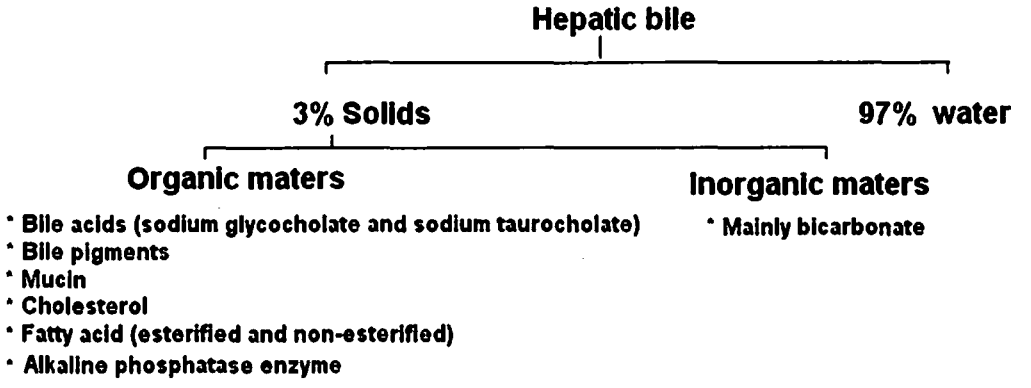
A. In between meals, sphincter of oddi is closed. Thus bile is stored in the gall bladder.

B. When the food enters the duodenum, the sphincter relaxes and the gall bladder contracts to evacuate its content.

C. **Physical properties of bile:**

1. **Volume:** 0.5 liter / day.
2. **pH:** 7.2

D. **Composition:**




E. **Gall bladder bile differs from hepatic bile in:-**

1. More concentrated (85% water only) due to absorption of water.
2. More acidic due to absorption of bicarbonate.

F. **Choleretics:**

These are substances which stimulate bile secretion: e.g. bile salts, protein diet and histamine are choleretics.

G. **Cholagogues:**

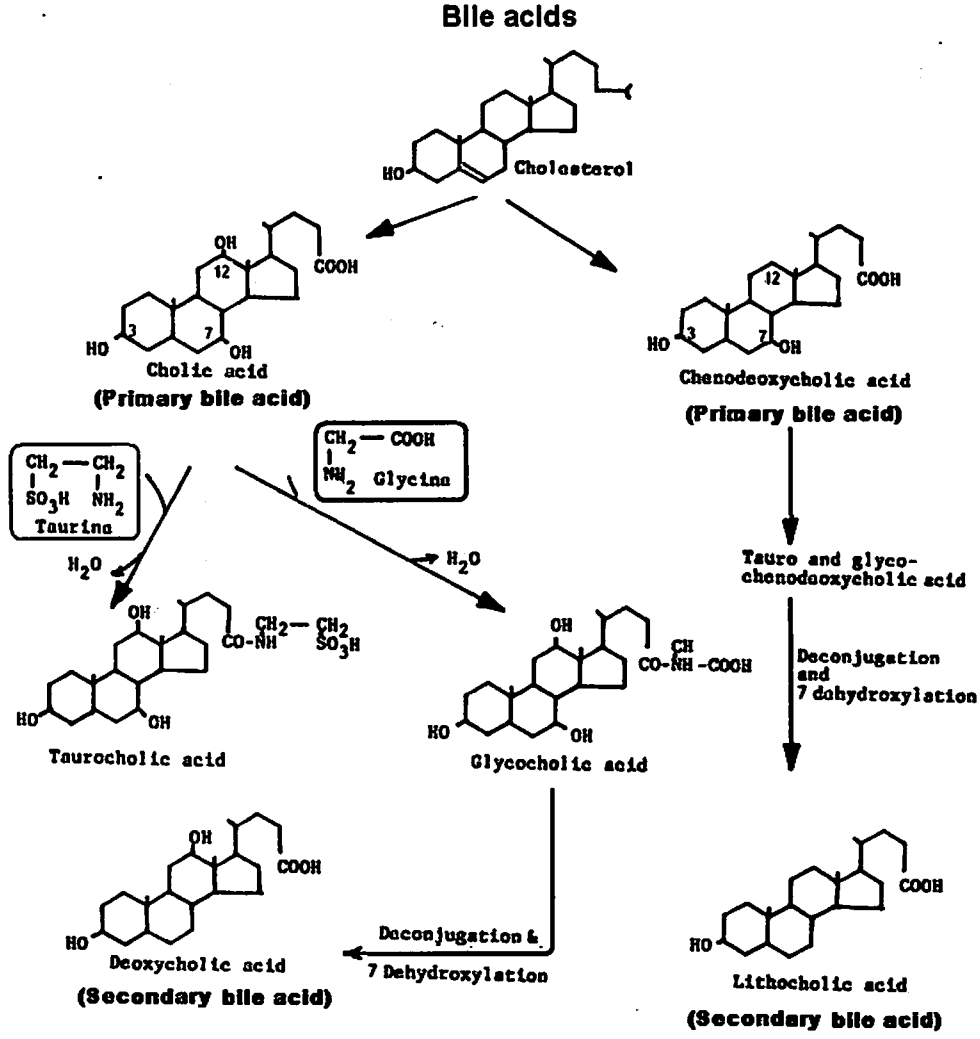
These are substances which stimulate contraction and evacuation of gall bladder e.g. bile salts, magnesium sulfate and cholecystokinine hormone are cholagogues.

## VI. *Bile acids*

A. **Formation and structure:**

1. Site: liver.
2. Precursor: cholesterol.
3. Mechanism: see diagram

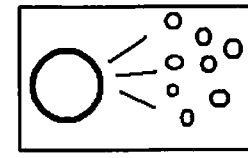
- Primary bile acids contain –OH at carbon number 7. Secondary bile acids contain no–OH at carbon number 7.
- The active form of bile acids are the sodium salt of both Glyco-and Taurocholic acids. The ratio of both in human bile is: 3 sodium glycocholate : 1 sodium taurocholate.




## B. Functions of bile salts:

1. **Digestion of lipids:**

   Bile salts help the emulsification of lipids (i.e. breakdown of large molecules into small ones). This increases the surface area upon which digestive enzymes act.



2. **Absorption of lipids:**

   Bile salts together with lipids forming the water soluble micelles. This help the absorption of lipids.

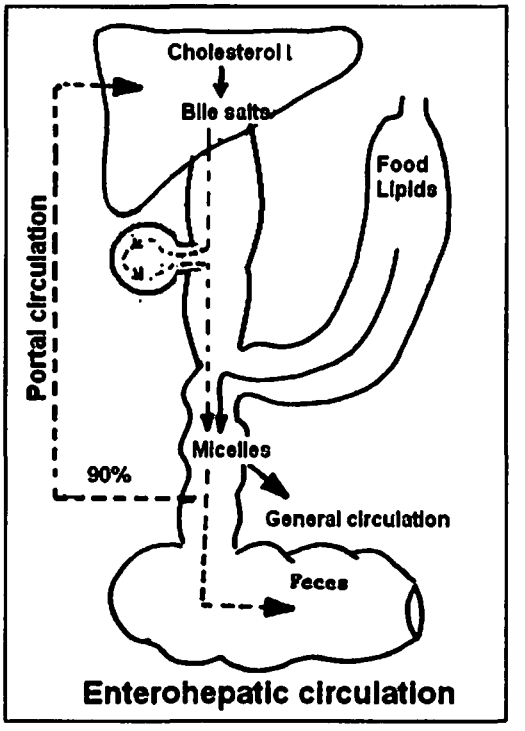
3. **Antiputrifactive action:**

   Bile acids inhibit the multiplication of pathogenic intestinal bacteria.

4. **Choleretic action:**

   Bile acids are absorbed again to the liver (by enterohepatic circulation) and stimulate the bile production.

## C. Enterohepatic circulation



Enterohepatic circulation

1. Bile acids are formed in the liver from cholesterol.
2. They conjugate with sodium glycine and sodium taurine forming bile salts.
3. Portion of bile salts together with water insoluble lipid form the micelles. Micelles are water soluble and they are absorbed along lymphatics to general circulation.
4. The second portion is partly deconjugated and dehydroxylated and reabsorbed in the ileum to the liver via portal circulation.
5. This cycle of excretion into bile, absorption from the intestine and re-excretion into the bile as known as enterohepatic circulation of bile acids.
6. It serves to return to the liver about 90% of bile acids secreted per day into the intestine.
7. A third portion escapes from absorption and passes to the large intestine to be excreted in feces. This portion is the major pathway for cholesterol excretion.

## D. Functions of bile:

1. **Bile acids:**
   - *a)* Digestion of lipids.....
   - *b)* Absorption of lipids.....
   - *c)* Choleretic action.....
   - *d)* Antiputrifactive action.

   } See before
2. **Neutralization of HCl:**
   Bile contains a high content of bicarbonate. This neutralizes any HCl escape to the intestine.
3. **Excretory function:**
   Many drugs, toxins, bile pigments and many inorganic substances are excreted into the bile.
4. Bile salts keep cholesterol in soluble form. This prevents cholesterol stone formation.

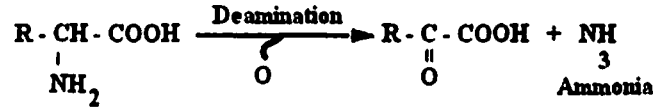
## VII. *Intestinal bacteria (flora), putrefaction and fermentation:*

**A.** Most of the ingested food is absorbed from the small intestine. The residue passes into the large intestine.

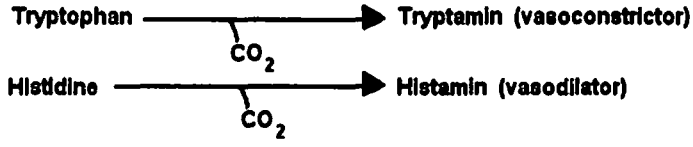
**B.** In the large intestine, absorption of more water takes place and the intestinal contents become more solid.

**C. Intestinal bacteria act on the solid material and result in the production of following:**

1. Production of **vitamin $B_{12}$** (not absorbed).
2. **Production of toxic substances:** they are formed mainly by putrefaction of protein.
3. **Production of some compounds through:**
   *a)* Conversion of cholic acid to deoxycholic acid.
   *b)* Conversion of chenodeoxycholic acid to lithocholic acid.
   *c)* Reduction of cholesterol to coprostanol.
   *d)* Reduction of bilirubin to sterchobilinogen.
4. <u>Intestinal fermentation:</u> The action of the intestinal bacteria on carbohydrate is known as fermentation, which produces
   *a)* **Acids:** a mixture of acids (formic, acetic, propionic, butyric and lactic acids)
   *b)* **Gases:** (carbon dioxide, hydrogen and methane)
5. <u>Intestinal putrefaction:</u>
   *a)* **Deamination:** Production of ammonia by deamination of amino acids.




   *b)* **decarboxylation:** Production of amines by decarboxylation of amino acids:




   *c)* **Production of Indole and skatole** by acting on tryptophan: Tryptophan undergoes a series of reactions to form indole and skatole. These substances are responsible for the foul odor of feces.
   *d)* **Production of ethyl mercaptan** ($CH_3$ -$CH_2$ -SH), **methyl mercaptan** ($CH_3$ -SH) and **hydrogen sulfide** ($H_2S$). This occurs by the action of intestinal bacteria on cysteine amino acids.

# Chapter 8 *Metabolism of xenobiotics*

## I. *Definition:*

A. **Xenobiotic:** is a compound that is foreign to the body. **Xenobiotics include:** drugs, insecticides and carcinogenic chemicals.

- **Xenos:** is a Greek word that means strange.

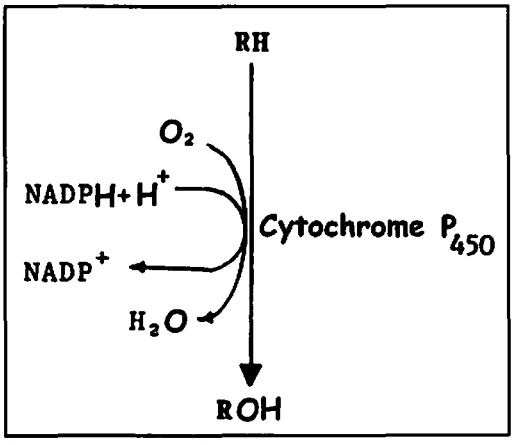
B. **Xenobiotic metabolism**: Are the biochemical reactions that involve the conversion of biologically active xenobiotics to less active or inactive compounds.

1. **Liver** is the main organ where metabolism of xenobiotics takes place.
2. In few cases, these reactions convert biologically inactive xenobiotics into active toxic forms.
3. Sometimes xenobiotics may be excreted unchanged.

## II. *Mechanism of xenobiotics metabolism*: This can be divided into two phases, hydroxylation and conjugation. Both phases aim to increase the solubility (polarity) of xenobiotics. This facilitates their excretion from the body.

A. **Phase I: Hydroxylation**:

1. Hydroxylation of xenobiotics (RH) increases their polarity and solubility.
2. Hydroxylation reactions include a variety of xenobiotics as drugs, carcinogens, pollutants and certain endogenous compounds as steroids.




3. The enzymes responsible for hydroxylation of xenobiotics are called **monooxygenase** or **cytochrome P-450 species.**

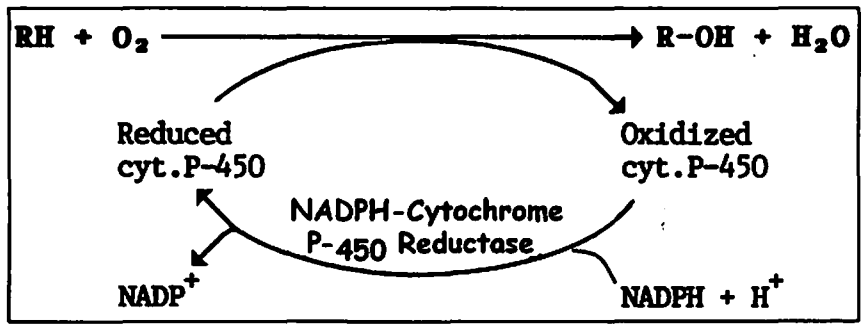
*a)* **Location:** These enzymes are present mainly in liver, These enzymes are present also in lung, kidney, gut, adrenal cortex, heart and brain.

*b)* **Types:** There are two types of cytochrome P-450:

1) **Mitochondrial:** This inactivates $O_2$ molecules.
2) **Microsomal:** This hydroxylates xenobiotics and mostly present in the endoplasmic reticulum (ER) of the liver cells.

*c)* **Characters:**

1) The name cytochrome P-450 is used because the enzyme preparations have a characteristic absorption peak at 450 nm when measured by spectrophotometer.
2) Like hemoglobin, cytochrome P-450 species are hemoproteins i.e. contain heme ring in their structure.
3) NADPH, not NADH is involved in the reaction of the cytochrome P-450.The enzyme that uses $NADPH^+$ to give the reduced cytochrome P-450 is called NADPH cytochrome P-450 reductase.



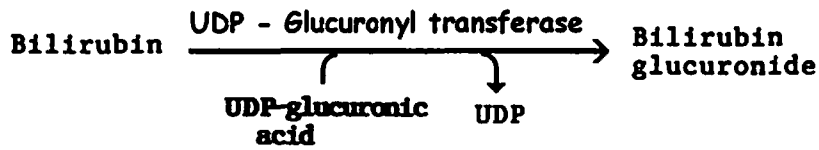

4) Most species of cytochrome P-450 are inducible i.e. their synthesis by liver cells is stimulated by administration of xenobiotics.

**B.** <u>**Phase II: Conjugation, acetylation and methylation:**</u> The more polar hydroxylated xenobiotics produced in phase I are conjugated, acetylated or methylated in phase II to give more soluble and less toxic compounds that easily excreted in urine or bile.

**1. Conjugation:** The conjugation reactions include:

*a)* **Glucuronidation** i.e. addition of glucuronic acid to xenobiotic.

1) UDP-Glucuronic acid is the glucuronyl donor.
2) The enzyme involved is UDP-glucuronyl transferase.
3) Bilirubin, aniline, benzoic acid, some carcinogens and many steroids are conjugated and excreted as glucuronides.



*b)* **Sulfation:** Some alcohols, phenols, steroids, glycolipids and glycoproteins are sulfated.

- The sulfate donor is active sulfate (adenosine-3' phosphate-5'phosphosulfate (PAPS).

*c)* **Conjugation with glutathione (G-SH):** Glutathione is a tripeptide formed of 3 amino acids: glutamate, cysteine and glycine.

1) Conjugation of glutathione with toxic xenobiotics (R) like some drugs and carcinogens renders them non toxic.

$$R\ (Toxic) + G\text{-}SH \xrightarrow{Glutathione\text{-}S\text{-}Transferase} R\text{-}SG\ (Nontoxic)$$

2) Glutathione-S-transferase enzyme is present in high concentration in **liver cytosol.**

3) If the toxic xenobiotics were not conjugated to G-SH, they would be free to combine covalently with DNA, RNA or cell protein and lead to serious cell damage.

2. **Acetylation:** is the addition of acetyl group to the xenobiotics (R).

$$R + Acetyl\ CoA \xrightarrow{Acetyl\ Transferase} Acetyl\text{-}R + CoA$$

*a)* The acetyl group donor is the acetyl CoA.

*b)* Acetyl transferase enzyme is present in cytosol of various tissues especially liver.

3. **Methylation:** is the addition of methyl ($-CH_3$) group to the xenobiotics (R).

$$R + S\text{-}Adenosyl\ methionine \xrightarrow{Methyl\ Transferase} R\text{-}CH_3 + S\text{-}Adenosyl\ homocysteine$$

*a)* The methyl donor is S-adenosyl methionine.

*b)* Methyl transferase enzyme is the enzyme responsible for methylation.

**III.*Effects (responses) of xenobiotics:*** Xenobiotics are metabolized in the body. Phase I reactions may produce their active forms or may diminish or terminate their actions. Some xenobiotics are very toxic or may be non toxic. Their toxic effects include:

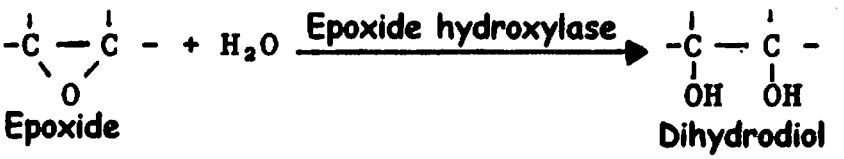
A. **Cell injury**, which can be severe leading to cell death.

- The mechanism is the covalent binding of xenobiotics to cellular protein, DNA or RNA. This may stop the cellular function.

B. **Antibodies formation**: xenobiotics may combine with some cellular proteins forming complex. This complex will stimulate the formation of antibodies against cells of the body leading to cellular injury.

C. **Carcinogenesis**: xenobiotics may act as chemical carcinogens causing DNA mutation and cancer.

1. Certain monooxygenase react with some carcinogenic xenobiotics forming compounds called **epoxides**. Epoxides are carcinogenic
2. Epoxides are converted into less reactive, non-carcinogenic compounds called dihydrodiol by the action of epoxide hydrolase enzyme.

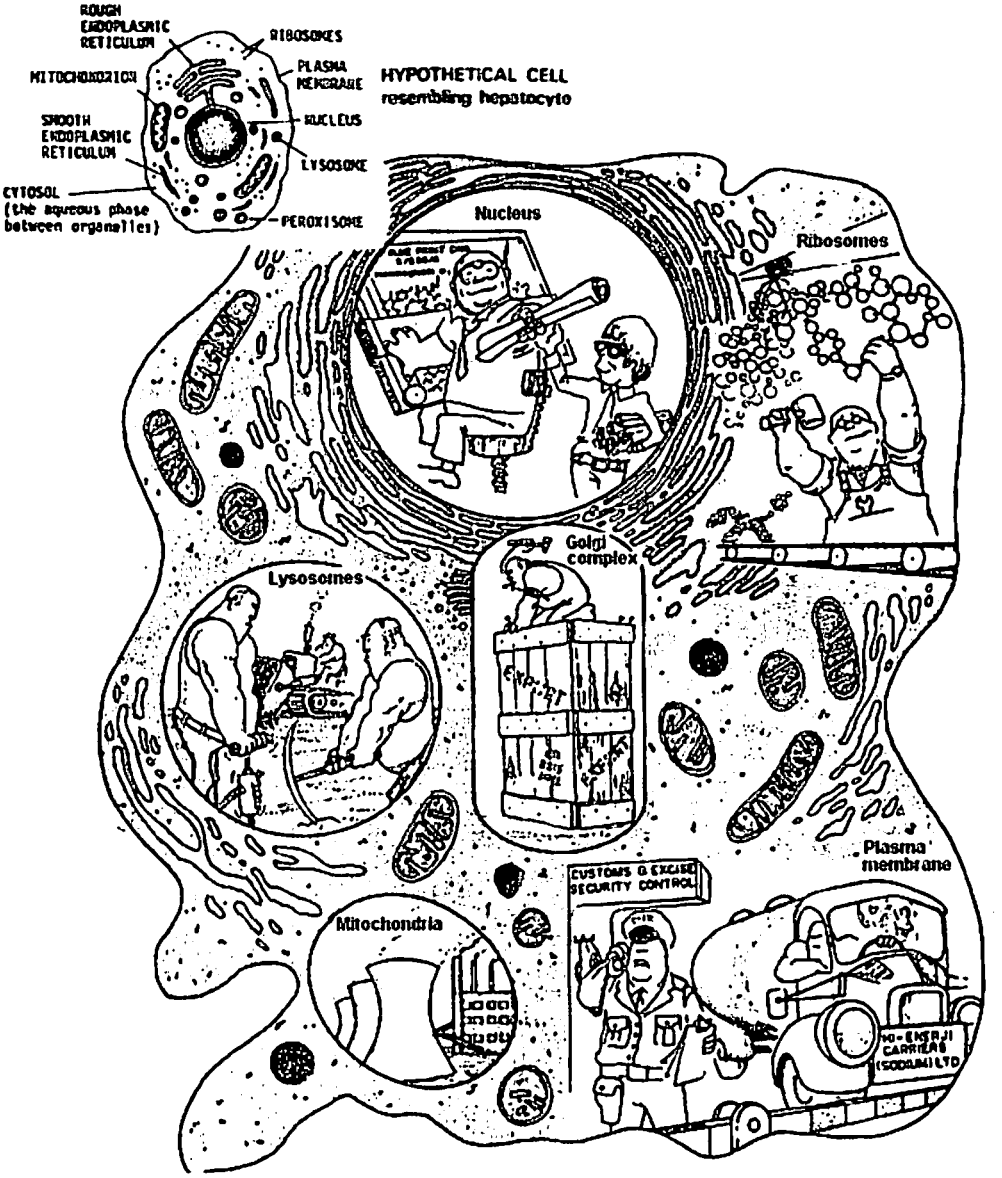



3. **Epoxide hydrolase enzyme is** present in the membrane of endoplasmic reticulum (ER) of liver and other tissues.

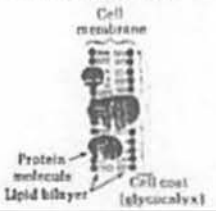
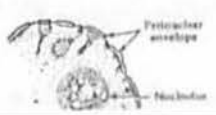
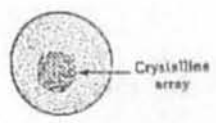
# Chapter 9 *Cell and cell membranes*

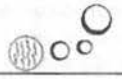
## I. *Introduction:*

Cell is the unit of a living system. Structurally it consists of an aggregate of molecules that enabling the survival and growth of the whole organism. Such molecules are composed chemically from nucleic acids, proteins, carbohydrates and lipids. Synthesis and breakdown of these molecules are located in certain cell organelles. These organelles are: cell membranes, nucleus, ribosomes, cytosol, mitochondria, Glogi apparatus, peroxisome, smooth and rough endoplasmic reticulum.



## II. *Structure and functions of different organelles:*

| Schematic drawing | Composition | Functions |
|---|---|---|
| Cell membrane   | It is composed of acid mucopolysaccharides, glycerolipids and glyco-proteins. | *Plasma membrane is selectively permeable.<br>*They carry cell receptors that enable the recognition of the cell by certain substances.<br>*It contains active transport system for $Na^+$ and $K^+$, glucose, amino acids as well as a number of important enzymes. |
| Nucleus  | *It is surrounded by perinuclear envelope.<br>*It is rich in DNA and RNA.<br>*DNA combines with histones and organized into chromosomes. | *During mitosis, chromosomes undergo replication of their DNA and separation into daughter chromosomes.<br>*DNA directs the protein biosynthesis inside the cell. |
| Ribosomes   | *Each ribosome has a large and a small subunits. Each subunit contains about 65% RNA and 35% protein. | *Ribosomes are the sites of protein synthesis. |
| Cytosol  | *It is the soluble fraction of cytoplasm. -It is highly viscous.<br>*The protein concentration is more than 20%. | *Most of the proteins of the cytosol are enzymes required in metabolism.<br>*Cytosol also contains metabolic intermediates and inorganic salts. |
| Mitochondria   | *There are about 800 mitochondria in liver cell.<br>*Their outer and inner membranes differ in lipids composition and enzymatic activity.<br>*matrix is rich in enzymes. | *The mitochondria are the power house of the cell.<br>*Carbohydrates, lipids and amino acids are oxidized to $CO_2$ and $H_2O$ by molecular $O_2$.<br>*The energy liberated is stored in ATP molecule.<br>*The enzymes of electron transport, energy liberation and ATP formation are located in the inner membrane. |
| Golgi apparatus   | *It consists of flattened, single membrane vesicles. Some become vacuoles in which secretory products are concentrated. | *Glogi apparatus functions in:<br>a-Packing the proteins synthesized in ribosomes.<br>b-Addition of non protein fragment to proteins e.g. addition of carbohydrate to protein to form glycoproteins, and addition of zinc to proinsulin to form insulin.<br>c- Helps the formation of plasma membrane and membranes of lysosomes.<br>d-Secretion of cell products such as proteins to outside the cell. |
| Lysosomes  | *Lysosomes are single membrane vesicles. They contain hydrolytic enzymes, such as ribonuclease and phosphatase. | *Lysosomes function in the digestion of materials brought into cell by phagocytosis or pinocytosis.<br>*They also serve to digest cell components after cell death. |
| Peroxisome   | *Microbodies are single membrane vesicles. They contain enzymes like catalase, D-amino acid oxidase and other oxidative enzymes. | *Peroxisomes share in the oxidation of certain nutrients.<br>*Hydrogen peroxide ($H_2O_2$) is converted into $H_2O$ and $O_2$ in peroxisomes. |

| | | |
|---|---|---|
| Smooth and rough endoplasmic reticulum  | *The endoplasmic reticulum consists of flattened, single membrane vesicles, whose inner compartments the cisternae, interconnected to form channels throughout the cytoplasm.<br>*Rough endoplasmic reticulum contain ribosomes on its surface. | *Rough endoplasmic reticulum is the site of protein biosynthesis.<br>*Smooth endoplasmic reticulum is the site of lipids synthesis. |
| Storage granules  | *These are polymer of sugars.<br>*Some bacteria contain granules of poly-β-hydroxy-butyric acid. | *When needed as fuel, these polymers are enzymatically degraded to yield free glucose or free -β-hydroxy- butyric acid. |

**N.B.**

Cytoplasm is consisted of all the components of a cell apart from the nucleus.

**III. *Types of living cells:*** Living cells may be subdivided into two groups.

| Eukaryotic cells | Prokaryotic cells |
|---|---|
| DNA within nuclear membrane. | DNA not included in nuclear membrane. |
| Contain mitochondria and/or chloroplasts. | No mitochondria |
| No cell wall | Contain cell wall of characteristic structure |
| Large ribosomes | Small ribosomes |
| Capable of pinocytosis i.e. taking liquids to form vesicles | Not capable of pinocytosis. |
| Examples:<br>a. Animals<br>b. Plants<br>c. Fungi<br>d. Protozoa | Examples:<br>a. Bacteria<br>b. Blue-green algae. |

## IV. *Functions of cell membrane:*

### A. Structural functions:

1. Cell membranes (also called plasma membranes) form enclosed compartments around cells. They separate the inside cells from external environment.
2. Membranes also may be formed around organelles e.g. nucleus and mitochondria.

### B. Metabolic functions:

1. Membranes contain specific molecular pumps and **gates.**
2. They contain specific **receptors,** which bind with different substances e.g. hormone receptors, lipid receptors.....etc.
3. Some membranes generate **signals, which** may be chemical or electric.
4. Membranes are the site of **energy production:**
   *a)* ATP production by oxidative phosphorylation in the inner mitochondrial membrane.

*b)* Photosynthesis of inner membrane of chloroplasts in plants.

## V. *Structure of membranes:*

Membranes are mainly formed of lipids, proteins and carbohydrates.

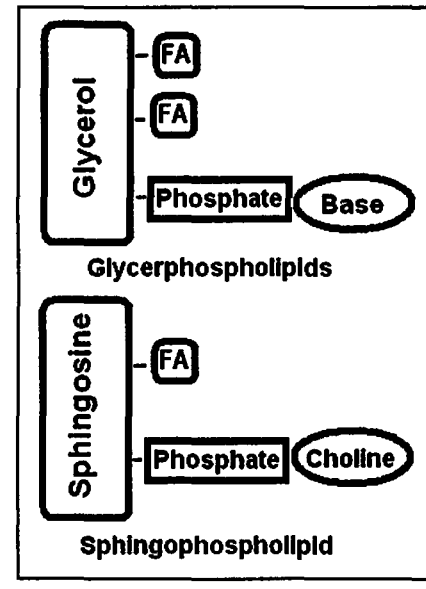
### A. Membrane lipids:

1. The membrane lipids include mainly phospholipids with less glycolipids and cholesterol.

*a)* **Phospholipids:**

1) **Glycerophospholipid:** (i.e. contain glycerol):
   - i- Fatty acids are mainly palmitate ($C_{16}$) and stearate ($C_{18}$).
   - ii- Bases are mainly choline, serine, ethanolamine and inositol.

2) **Sphingophospholipids:** (i.e. contain sphingosine):
   - i- Only one type called: sphingomyeline, which contains choline base.
   - ii- It is present mainly in myelin sheath.




*b)* **Glycolipids:**

These are lipids containing sugar. These are mainly in the form of:

1) **Cerebrosides:** contain one sugar unit e.g. glucose or galactose:
2) **Gangliosides:** contain 3 or more sugar units.

*c)* **Cholesterol:**

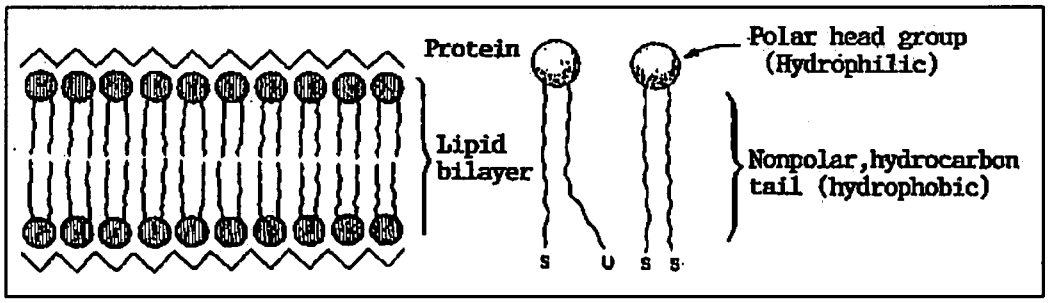
It is present mainly in plasma membrane, and lesser amount is present in mitochondrial and nuclear membranes.

2. **Lipid bilayer membranes:**

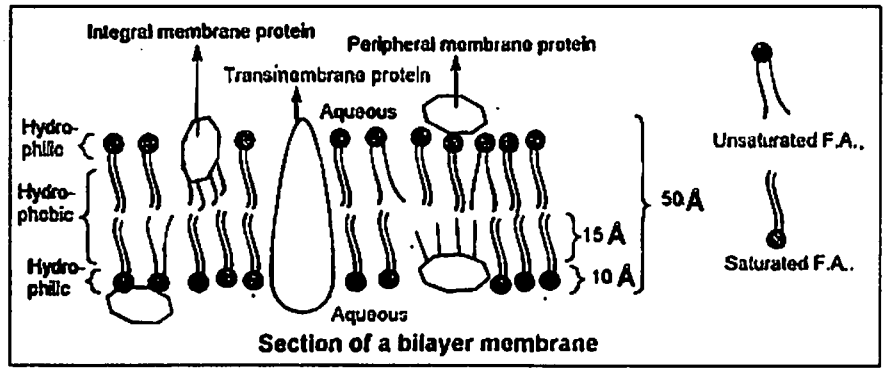
*a)* Lipids **have polar** (hydrophilic) head group and **nonpolar** (hydrophobic) tail group i.e. they are amphipathic.

*b)* In aqueous solution, membrane phospholipids are arranged in bilayer form, where the polar groups are arranged outside, while nonpolar groups are arranged inside.

*c)* Fatty acids content of phospholipids are either saturated with straight tails or unsaturated with kinked tail. The more kinks present (less tightly packed), the more fluidity of the membrane.




*d)* Each half of the lipid bilayer is 25 angstroms (Å) thick, with the head portion 10 (Å) and the tail portion 15 (Å).Total thickness (2 halves) is about 50 (Å).




3. **Stability of lipid bilayer:**

   It is stabilized by the following forces:

   *a)* **Hydrophobic interactions:** major force.

   *b)* **Van Der Waals attractive forces:** between the hydrocarbon tails.

   *c)* **Electrostatic and hydrogen bonding:** between the polar head group and water **molecules.**

4. **Membrane lipids are responsible for:**

   *a)* **Fluidity:**

   1) **Definition:** Ability of cell membrane components for movement.

   2) **It depends on** both temperature and lipid contents:

      i- The more temperature, the more fluidity.

      ii- The more unsaturated fatty acids, the more fluidity.

      iii- The more cholesterol content, the more fluidity in the hydrophobic core and less fluidity in the hydrophilic core.

   *b)* **Selective permeability:**

   1) Ionic and polar substances cannot pass cell membrane freely. This is due to the hydrophobic nature of the hydrocarbon chain in lipid bilayer.

   2) These substances can go out and in of all cells by specific membrane proteins.

*c)* **Asymmetry:**

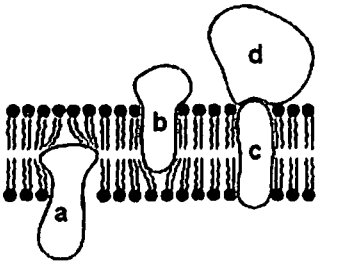
1) **Definition:** It means that the lipid components of each half of the bilayer is different from the other. Also carbohydrates and proteins are irregularly distributed.
2) **Causes of membrane asymmetry:**
   - i- Phospholipids containing choline are located mainly in the outer layer, while phospholipids containing amino group e.g. phosphatidyl serine are located mainly in the inner layer.
   - ii- Carbohydrate content are located mainly in the out-layer.
   - iii- Protein content are irregularly distributed in the membrane. Many proteins e.g. hormone receptors are located in outer layer.

**B. <u>Membrane proteins:</u>**

1. **Types:** Two types; peripheral and integral:

*a)* **Peripheral membrane proteins:**

1) Weakly bound to surfaces of integral membrane proteins.
2) They can be removed by salt solution without disturbing membrane.

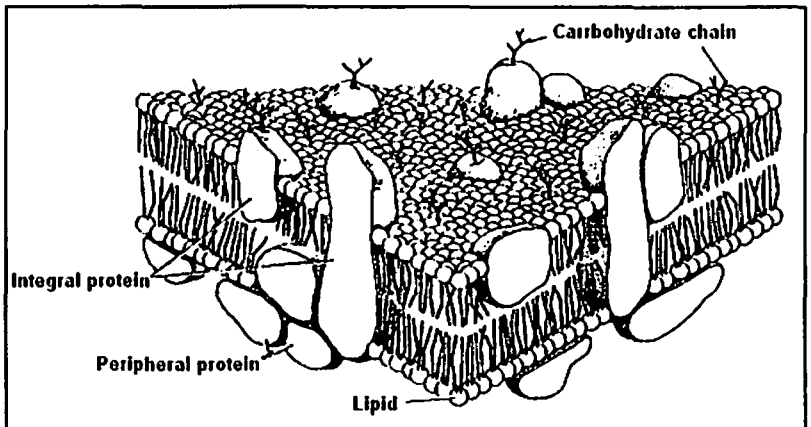



**Integral membrane proteins (a, b,c) interact extensively with the hydrocarbon region of the bilayer. Peripheral membrane proteins (d) bind to the surface of integral membrane proteins.**

*b)* **Integral membrane (transmembrane proteins):**

1) They are deeply embedded in the lipid bilayer.
2) They are attached by Van Der Waals forces and removed by detergent.

2. **Fluid mosaic model:**




**The fluid mosiac model of membrane structure**

Membrane phospholipids act as a solvent for membrane proteins, forming an environment in which proteins can function. Most of proteins have 2 hydrophilic ends separated by a hydrophobic region which traverses the hydrophobic core of the phospholipid bilayer (fluid mosaic model).

3. **Functions of membrane proteins:**
   They carry out most membrane processes as:
   *a)* Transport of substances and communication.
   *b)* Cell membrane receptors.
   *c)* Immunoglobulins are integral proteins of membranes of lymphocytes which can be released and circulating in the blood.
   *d)* Proteins of mitochondrial membrane are essential for energy production (ATP).
   *e)* Many enzymes are membrane bound.
   *f)* Erythrocyte membrane proteins have important functions.

4. **Erythrocyte membrane:** Contain specific proteins which include:
   *a)* **Ankyrin and spectrin:**
      1) They are peripheral proteins bound together within red cell membrane.
      2) They maintain the biconcave shape of red cells.
      3) Mutation of gene of spectrin results in a disease called **hereditary spherocytosis** where there is loss of biconcave shape of red cells → Hemolysis → Hemolytic anemia

   **Erythrocyte membrane proteins:**
   - **Ankyrin and spectrin**
   - **Glycophorin**
   - **Anion protein channel**

   *b)* **Glycophorin:**
      1) It is integral protein (glycoprotein):
         i- The protein part is formed of a single polypeptide chain.
         ii- Carbohydrate part (60% of glycophorin) is formed of 16 sugar units (oligosaccharide). It is rich in sialic acid.
      2) **Functions of glycophorin:**
         i- Constitute the blood group substances (ABO).
         ii- Glycophorin give red cells a very hydrophilic charged coat which enables them to circulate without adhering to other cells and vessel walls.

*c)* **Anion channel protein:**

1) It consists of 2 identical subunits.
2) It plays an important role in transport of $CO_2$ via blood.

### C. Membrane carbohydrates:

1. They are present in the form of glycoproteins and glycolipids. They are located on the external surface of cell membrane.
2. **Functions of membrane carbohydrate:**
   *a)* **Receptors:** in the form of glycoprotein.
   *b)* **Glycophorin:** is a glycoprotein present in red cell membrane (see before).
   *c)* **Glycoprotein of ovum** which is essential for recognition by sperm receptors. This is important for fertilization.

## VI. *Transport across membranes:*

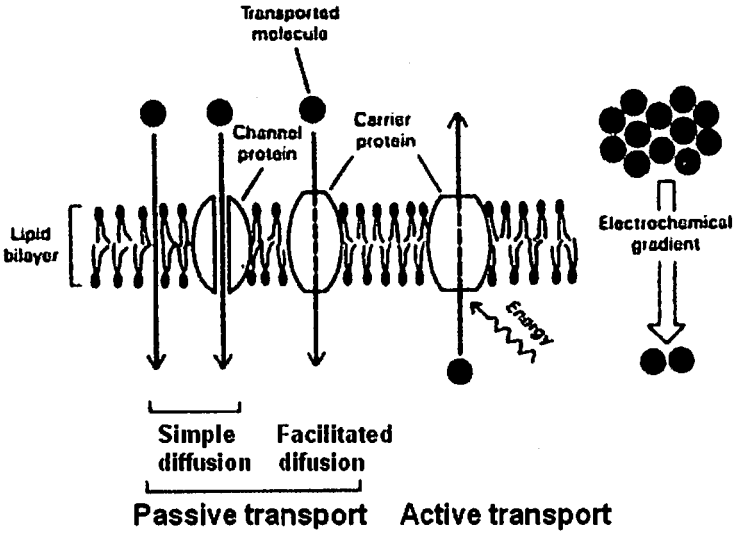
Molecules can be transported across membranes by the following mechanisms:

| | |
|---|---|
| **A- Transfer of small molecules:** | |
| 1. Passive (simple) diffusion. | Simple diffusion |
| 2. Facilitated (simple) diffusion. | |
| 3. Active transport. | |
| **B- Transfer of large molecules:** | |
| 1. Endocytosis. | |
| 2. Exocytosis. | |

### A. Transfer of small molecules:

1. **Passive (simple) diffusion:**
   *a)* Substances move from higher to lower concentration i.e. according to concentration gradient.
   *b)* Needs no energy.
   *c)* Rate of transport depends on solubility of the transported molecules in the hydrophobic core of the membrane.
   *d)* Transmembrane channels, which are protein containing pores is another example of passive transport.

1) they transport several species of similar size and charge e.g. $Na^+$,$K^+$....
2) Some channels are open continuously. Other ($Ca^{++}$ channels) open only in response to specific signal so called gated channels.




**2. Facilitated (simple) diffusion:**

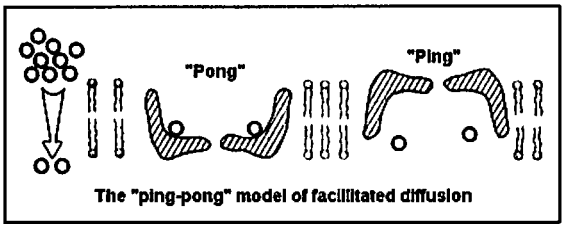
*a)* Means transport of small molecules by specific carrier proteins e.g. glucose carrier protein. It needs no energy.

*b)* Facilitated diffusion differs from passive diffusion in that it can be saturated i.e. diffusion stops when all carriers are saturated with transported molecules.

*c)* **Ping Pong model for facilitated diffusion:**

Carrier proteins can exists in 2 configurations: ping and pong states.

1) **In pong state:** The active sites of carrier proteins are faced to exterior. When the transported molecules bind to specific sites, carrier proteins will undergo conformational changes, and converted into ping state.




2) **In ping state:** The active sites are faced to interior of the cell, when the concentration of transported molecules is minimal. This will cause release of the solutes and the carrier proteins return to pong state.

3) **Factors affecting facilitated diffusion:**

i- Amount of carrier proteins.

ii- Affinity of the transported molecules to the carrier proteins.

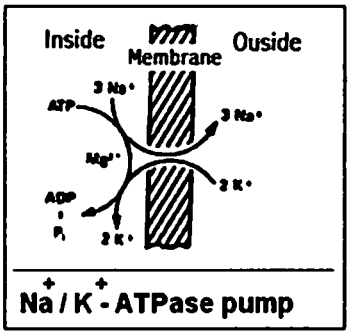
iii- Rapidity of conformational changes.

iv- Hormones e.g. insulin increase the glucose carrier proteins.

**3. Active transport:**

*a)* Substances move from lower concentration to higher concentration.

*b)* It needs energy, which can gained from sodium-potassium pump, where there is hydrolysis of ATP in the presence of ATPase enzyme. This enzyme is a part of cell membrane proteins.




**B. <u>Transfer of large molecules:</u>**

**1. Endocytosis:**

*a)* Is the process by which cells take up large molecules.

*b)* The cell internalizes extracellular macromolecules to form endocytic vesicle.

*c)* There are two types of endocytosis.

1) **Pinocytosis (cell drinking):**

i- It occurs in all cells and leads to cellular uptake of fluid.

ii- Liver uptake chylomicrones and LDL by pinocytosis.

2) **Phagocytosis (cell eating):**

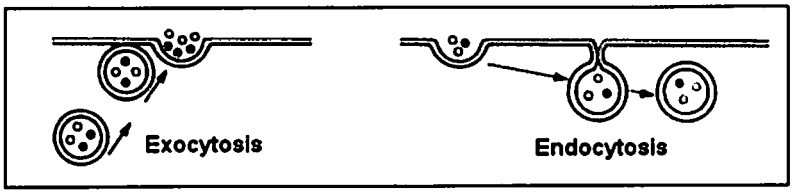
i- It occurs only in specialized cells as macrophages and granulocytes as they ingest bacteria.

ii- They extend pseudopodia and surround the bacteria to form phagosomes which fuse with lysosome forming phagolysosomes inside which the particles are digested.

**2. Exocytosis:**

*a)* It is an opposite process of endocytosis.

*b)* It is used to release macromolecules made in the endoplasmic reticulum and Golgi apparatus to the outside of the cell e.g. release of insulin hormone from β-cells of islets of Langerhans in pancreas.

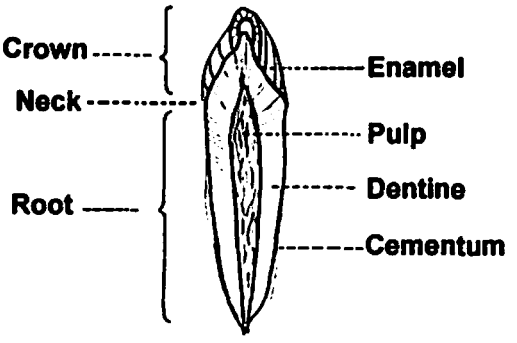


# Chapter 10 *Biochemistry of teeth*

I. The teeth cut, grind and mix the food eaten. The following figure illustrates a sagittal section of tooth. It shows its major functional parts: the enamel, dentine, Cementum and pulp.

II. ***Structure:***

The tooth can be divided into the crown, which is the portion that protrudes out the gum into the mouth, and the root, which is the portion that protrudes into the bony socket of the jaw. The collar between the crown and the root where the tooth is surrounded by the gum is called the neck.



**Functional parts of a tooth**

A. **Dentine:**

1. Dentine forms the main body of the tooth.
2. It is made up of:
   *a)* **Hydroxyapatite crystals:**
   These are crystals formed of 3 molecules of calcium phosphate and one molecule of calcium hydroxide: 3 $Ca_3(PO_4)_2$ .Ca $(OH)_2$.
   *b)* **Collagen:**
      1) It is one of scleroproteins that are rich in glycine, proline, hydroxyproline and hydroxylysine.
      2) The calcium salts in dentine make it extremely resistant to compression forces, while the collagen fibers make it tough and resistant to tensional forces.

B. **Enamel:**

1. It is the hardest tissue in the body and contains only 3% water.
2. It is made up of:
   *a)* **Hydroxyapatite crystals:**
   Together with adsorbed carbonate, magnesium, sodium, potassium and other ions. The crystalline structure of the salts makes the enamel extremely hard and much harder than the dentine.

*b)* **Keratin:**

It is another member of scleroproteins that rich in cysteine. It is very strong and almost completely insoluble protein fibers. Keratin makes enamel very resistant to acids, enzymes and other corrosive agents.

C. **Cementum**: Cementum is a bony substance that holds the tooth in place.

D. **Pulp**: The inside of each tooth is filled with pulp which in turn is composed of connective tissue with an abundant supply of nerves, blood vessels and lymphatics.

## III. *Factors affecting the development of teeth:*

A. **Hormones**: Thyroid and growth hormones accelerate the speed of eruption of teeth.

B. **Diet**: Diet is rich in calcium and phosphate help the deposition of salts in the early forming teeth.

C. **Vitamins**: Vitamin D is essential for calcification of teeth.

## IV. *Mineral exchange in teeth*

The salts of teeth, like those of bone, are composed basically of hydroxyapatite with adsorbed carbonates and various cations bound together in a hard crystalline substance. Also, new salts are constantly deposited while old salts are being reabsorbed from the teeth (as occurs in bones).

## V. *Biochemical aspect of dental caries*

A. Dental caries means erosion and structural damage of teeth.

B. **Mechanism of dental caries:**

1. Bacteria are normally present in the mouth.
2. The bacteria convert all foods - especially sugar and starch - into acids.
3. Bacteria, acid, food debris, and saliva combine in the mouth to form a sticky substance called plaque that adheres to the teeth. It is most prominent on the back molars, just above the gum line on all teeth, and at the edges of fillings.
4. Plaque, that is not removed from the teeth mineralizes into tartar. Plaque and tartar irritate the gums, resulting in gingivitis and ultimately periodontitis.
5. The acid in plaque dissolve the enamel surface of the tooth and create holes in the tooth (cavities).

6. Cavities are usually painless until they grow very large and affect nerves or cause a tooth fracture.
7. If left untreated, a tooth abscess can develop. Untreated tooth decay also destroys the internal structures of the tooth (pulp) and ultimately causes the loss of the tooth.
8. Carbohydrates (sugars and starches) increase the risk of tooth decay. Sticky foods are more harmful than nonsticky foods because they remain on the surface of the teeth. Frequent snacking increases the time that acids are in contact with the surface of the tooth.

### C. Prevention of caries by fluorine:

Small amounts of fluorine in water make the teeth more resistant to caries. This is because:

1. Fluorine replaces (OH) group of hyroxyapatite to form 3 $Ca_3(PO_4)_2$. Ca $(Fl)_2$. These new crystals are several times less soluble in acid medium.
2. Fluorine might be toxic to some of bacteria.

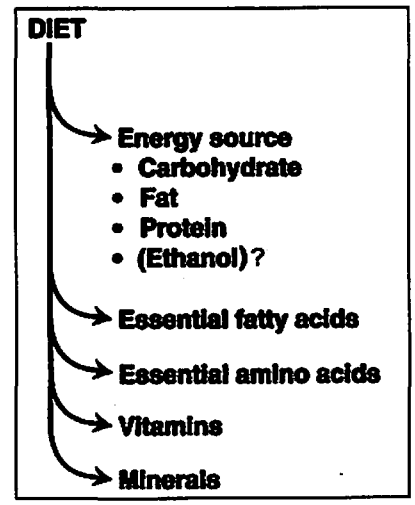
# Chapter 11 *Nutrition*

## I. *Introduction:*

A. The science of nutrition deals with the qualitative and quantitative requirements of the nutrients (diet) that maintain the normal function of the body.

B. **Functions of nutrients (diet)**: nutrients provides:

1. **Energy.**
2. **Essential molecules** that either cannot be synthesized by the tissues or synthesized in amounts not sufficient to support growth and maintenance. These essential nutrients include essential amino acids, essential fatty acids, vitamins and minerals.



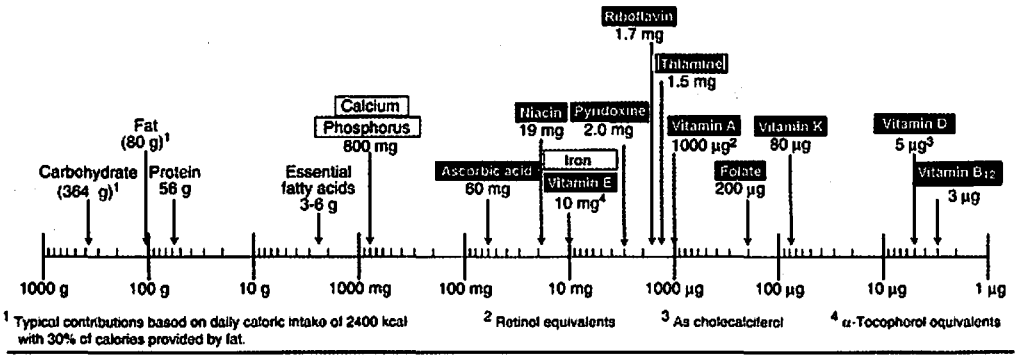

C. Food intake in excess of energy **expenditure** leads to **obesity**, while intake less than expenditure leads to **undernutrition** and wasting. Both obesity and undernutrition lead to diseases and even death.

D. **Body mass index**:

It is defined as weight in kilograms divided by height in meters squared. It is used as a way of expressing relative obesity to height. The desirable range is between **20** and **25**.

$$BMI = \frac{\text{Body wight (Kg)}}{\text{Hight (m) X Hight (m)}}$$

## II. *Nutrient requirements in human:*




Recommended dietary allowances for selected nutrients for 70 kg males, age 25 to 50.
Vitamins shown in black boxes; minerals shown in white boxes.

**A. The recommended dietary allowance (RDA):**

It is U.S. system designed as an estimate of the amount of a nutrients required for the needs of 95% of the U.S. population. Such design is not available in our eastern countries (see diagram).

**B. Factors affecting nutrients requirements:**

1. **Age:** nutrients requirements vary from infancy to adulthood. For example, adults require about 0.8 gram of protein per kg body weight, whereas infants need over 2.0 grams per kg body weight per day.
2. **Sex:** nutrients requirements for **men** are approximately 20% greater than those for **women**. This is due to the larger body mass of men. The iron requirement is an exception, because women must replace iron lost during menstruation.
3. **Other factors:**
   a) **Pregnant and lactating women:** need about 20-30% of most nutrients above normal individuals.
   b) **Patients with injury or illness:** show also an increased requirement for some nutrients.

**C. Adequacy of diet:**

Adequate diet should be **balanced** in verities and amounts and designed to maintain optimal health and to prevent chronic diseases. **Balanced diet should contain:**

1. **Water:** The most critical component of the diet.
2. **Energy:** Supplied by utilization of carbohydrates, fats and proteins in variable proportions.
3. **Amino acids:**
   *a)* **Essential amino acids**, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, valine, tryptophan and arginine.
   *b)* **Non-essential amino acids** are needed by the body but they can be formed in the body.
4. **Fatty acids:** Essential fatty acids e.g. arachidonic, linoleic and linolenic fatty acids.
5. **Vitamins:**
   *a)* **Water soluble:** ascorbic acid (C), thiamin ($B_1$), riboflavin ($B_2$), niacin, pyridoxine ($B_6$), biotin, pantothenic acid, cobalamine ($B_{12}$) and folic acid.

*b)* **Fat soluble vitamin:** A, D and E. ***Vitamin K*** is synthesized by intestinal microorganisms, therefore dietary requirement is uncertain.

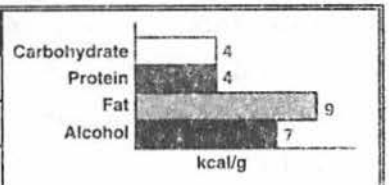
6. **Minerals:**
   *a)* **Macrominerals:** calcium, chloride, magnesium, phosphorus, potassium and sodium.
   *b)* **Microminerals "trace elements"**: chromium, copper, iron, iodine, manganese, molybdenum, selenium and zinc.
7. **Fibers:** Required for optimal health.

## III. ***Energy requirements in human:***

### A. Energy requirements of the food:

1. The energy content of food is calculated from the heat released by the total combustion of food in a calorimeter.
2. It is expressed in kilocalories (kcal or cal). [Note: the Joule (J) is a unit of energy widely used in many countries, (1 kcal = 4.128 kJ).
3. The amount of energy in carbohydrate, protein and fat is shown in the following table. Note that the energy content of fat is more than twice that of carbohydrate and protein.

| | Energy kcal / g | RQ |
|---|---|---|
| **Carbohydrate** | 4 | 1.00 |
| **Protein** | 4 | 0.81 |
| **Fat** | 9 | 0.71 |
| **Alcohol (ethanol)** | 7 | |




### B. The recommended energy requirement for average human is as follows:

| | AGE (YEARS) | WEIGHT (KG) | ENERGY NEEDS Mean | Range |
|---|---|---|---|---|
| **Men** | 23-50 | 70 | 2900 | 2300-3100 |
| **Women** | 23-50 | 50 | 2200 | 1600-2400 |
| **Pregnant** | ---- | ---- | 2500 | 1900-2700 |
| **Lactating** | ---- | ---- | 2700 | 2100-2900 |

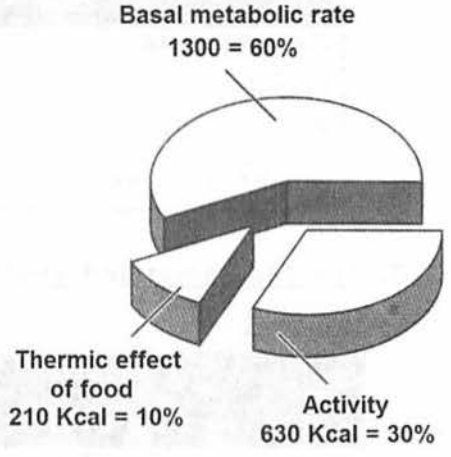
### C. Estimation of energy requirements:

1. Energy requirements are estimated by measurement of energy expenditure.

2. Under conditions of energy equilibrium (caloric balance), energy intake must equal energy expenditure.
3. **Methods of determination of energy expenditure:**
   a) Directly by measuring heat output from the body.
   b) Indirectly from the consumption of oxygen:
      1) Under most conditions, one liter of oxygen consumed account for approximately 4.85 kcal (20kJ) of energy expenditure.
      2) Measurement of the volume of carbon dioxide ($CO_2$) produced to volume of oxygen consumed (respiratory quotient: RQ), an indication of the mixture of metabolic fuel (carbohydrate, protein or lipid) being oxidized.
   c) A more recent technique permits estimation of total energy expenditure over a period of 1-2 weeks using **isotopically** labeled water $^{2}H_2{}^{18}O$.
      1) $^{2}H$ is lost from the body only in water.
      2) $^{18}O$ is lost in both water and carbon dioxide.
      3) The difference in the rate of loss of the two labels permits estimation of total carbon dioxide production and thus oxygen consumption and energy expenditure.

## D. Factors determining energy expenditure:

The total energy required by an individual is the sum of three energy-requiring processes that occur in the body: basal metabolic rate, thermic effect of the food (formerly termed specific dynamic action) and physical activity.




**Estimated energy consumption in a typical 20-year old women, 165 cm tall, weighing 50 kg and engaged in light activity.**

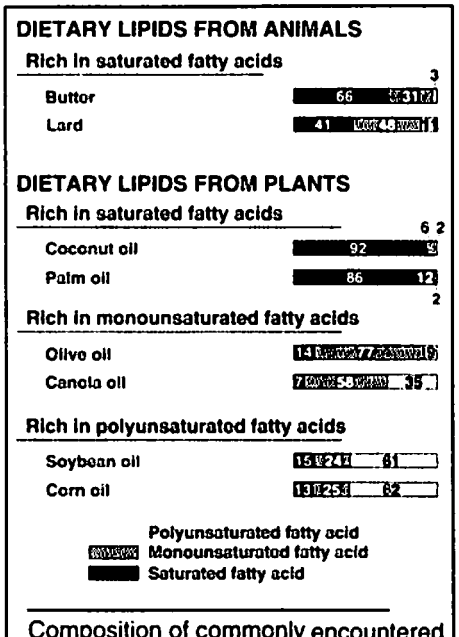
1. **Basal metabolic rate (BMR):**
   a) It is the energy expended by individual in resting condition (but not asleep) and in postabsorptive state (12 hours after last meal).
   b) It represents the energy required to carry out the normal body functions such as respiration, blood flow and neuromuscular integrity.
   c) It accounts about 60% of the daily energy expenditure in sedentary individuals.

2. **Thermic effect of food:**
   a) It is the energy needed for secreting digestion enzymes and active transport of the products of digestion. It is also the energy needed for storage of glycogen, triacylglycerols and protein.
   b) It accounts about 5-10% of the total daily energy expenditure.
3. **Physical activity:**
   a) The amount of energy consumed depends on the duration and intensity of the exercise.
   b) A sedentary person requires about 30-50% more than the basal caloric requirement of energy.
   c) Highly active individual may require 100% more calories above BMR.

IV. ***Macronutrients requirements in human:*** All energy in the diet is provided by three nutrients: lipids, carbohydrate and proteins:

A. **Lipids**:

1. Triacylglycerols constitute more than 90% of total dietary lipids.
2. **Importance of lipids in diet:**
   a) **Energy production:** however this is not essential function as other dietary sources can supply energy.
   b) **Essential polyunsaturated fatty acids**: lenoleic, lenolenic and arachidonic acids:
      1) These acids cannot be synthesized by the body and should be taken in diet.
      2) They have many biological functions as eicosanoids synthesis. They are required for membrane structure (see lipids chemistry).
   c) **Fat soluble vitamins (A, D, K and E)**: are supplied and absorbed with lipids.
   d) **Palatability of food**: the presence of fats in food makes it more palatable.




Composition of commonly encountered dietary lipids.

3. **Types of lipids in diet:**
   a) **Fats from plant sources:**
      1) Triacylglycerols obtained from plants generally contain more unsaturated fatty acids than those from animal sources. They are liquid at room temperature.
      2) Coconut and palm oils are exceptions and consisted mainly of saturated fatty acids.
      3) Olive oil and canola oil are fats rich in more unsaturated fatty acids.
      4) Corn oil and soybean oil are fats rich in polyunsaturated fatty acids.
   b) **Fats from animal sources:**
      1) They are derived from milk products, hard margarine, lards and meat remnants.
      2) They are generally contains saturated fatty acids.
      3) **Fishes are exception**, whose fatty acids are largely unsaturated.
   c) **Cholesterol** found only in foods of animal origin. It is very rich in egg yolk and organ meats.
4. **Lipids and diseases:**
   a) **Coronary heart diseases:**
      1) There is a strong correlation between coronary heart diseases, myocardial infraction, blood cholesterol and consumption of fat particularly of saturated fat.
      2) Ingestion of saturated fatty acids in diet is associated with high level of plasma cholesterol and LDL-cholesterol → Atherosclerosis.
      3) Ingestion of ω-6 and ω-3 polyunsaturated and monounsaturated fatty acids lower plasma cholesterol → protect against atherosclerosis.
   b) **Cancer: High intakes of saturated fats are associated with increase risk of certain cancers, especially cancer of colon, prostate and breast.**

## B. Carbohydrate:

1. Carbohydrates in the diet are classified as monosaccharides, disaccharides, polysaccharides and fibers. The metabolism of carbohydrate is discussed in part II.
   a) **Monosaccharides:** glucose and fructose are principle monosaccharides present in food.
      1) **Glucose:** is abundant in fruits e.g. grape, sweet corn, corn syrup and honey.

2) **Fructose (free):** is found together with free glucose and sucrose in honey and fruits.

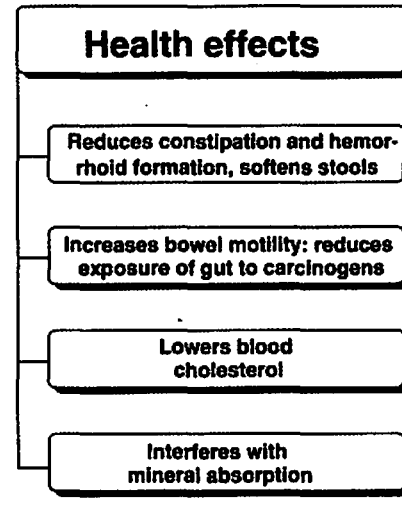
b) **Disaccharides:**

1) **Sucrose** (glucose + fructose): ordinary table sugar. Also it is abundant in cane, beef, molasses and maple syrup.
2) **Lactose** (glucose + galactose): milk sugar.
3) **Maltose** (glucose + glucose): it is a product of enzymatic digestion of polysaccharides. It is found also in beer and malt liquors.

c) **Polysaccharides:** Starch: polymer of glucose that do not have sweet taste. It is found in abundant in plants as wheat, other grains, potatoes, dried peas, beans and vegetables.

d) **Fiber:** Dietary fiber consists of non-digestible carbohydrates including cellulose, protein, gums, lignin and pentosans. Dietary fiber provides no energy, but has the following functions:

1) It adds bulk to diet, making little room for more traditional high fat and high cholesterol food.
2) Fiber can absorb 10 to 15 times its own weight in water, drawing fluid into the lumen of the intestine. **This prevents constipation by:**
   - Increasing bowel motility.
   - Producing of larger and softer feces.




Actions of dietary fiber.

3) The biding properties of fiber can result in decrease **absorption of toxic compounds**, including carbon substances causing cancers.
4) A high fiber diet is associated with reduced incidence of some disease e.g. **cancer colon**.
5) The more soluble fibers as gum and pentosans found in legumes and fruits, lower blood cholesterol, possibly by binding bile acids.
6) The more soluble fibers also slow stomach emptying, and they delay and alternate the postprandial rise in blood

glucose. This leads to decrease the amount of insulin required. This effect is beneficial to diabetics dieters.

7) However, dietary fiber can bind trace elements (e.g. zinc) and decrease the absorption of fat soluble vitamins. Thus, supplementation of the diet with moderate and not excess fiber is recommended.

2. **Requirements for carbohydrates:**

a) Carbohydrate is not an essential nutrient, because the carbon skeletons of amino acids can be converted into glucose (gluconeogenesis).

b) However, the absence of carbohydrates leads to:

1) Ketone bodies production.

2) Degradation of body proteins.

c) Thus, minimal daily intake of carbohydrate (50-100 grams) is recommended in human to prevent ketosis and save body proteins.

## C. Protein:

1. **Dietary proteins provide the body with essential amino acids:**

a) Ten of the 20 amino acids needed for the synthesis of body proteins are essential. That is, they cannot be synthesized in humans, and must be taken in diet.

b) Of ten essential amino acids, eight are essential at all times, whereas two (arginine and histidine) are required only during periods of rapid tissue growth characteristic of childhood or recovery from illness.

| Source | Biologic value |
|---|---|
| **Animal proteins** | |
| Egg | 100 |
| Beef | 100 |
| Fish | 87 |
| Milk | 85 |
| **Plant proteins** | |
| Soybean meal | 67 |
| Potato | 67 |
| Whole wheat bread | 30 |

Biologic value of some common dietary proteins (BV units).

2. **Biological value of proteins:** It is the ability of protein to provide the essential amino acids required for tissue maintenance.

a) ***Protein from animal sources:*** egg albumin, meat, poultry, milk, fish have a high biological value because they contain all essential amino acids.

b) ***Proteins from plant sources***: proteins from wheat, corn, rice and beans have a lower biologic value than animal proteins. That is because they are usually deficient in some essential amino acids.

e.g. corn is deficient in lysine. A mixture of plant food may compensate each other.

3. **Nitrogen balance:**
   a) *Nitrogen balance* means that nitrogen intake is equal to nitrogen loss from the body.
      1) **Nitrogen intake:** Nitrogen is taken in the form of dietary proteins. Every 100 g protein contain 16 g nitrogen.
      2) **Nitrogen loss:** Nitrogen is lost from the body through:
         - **In urine:**

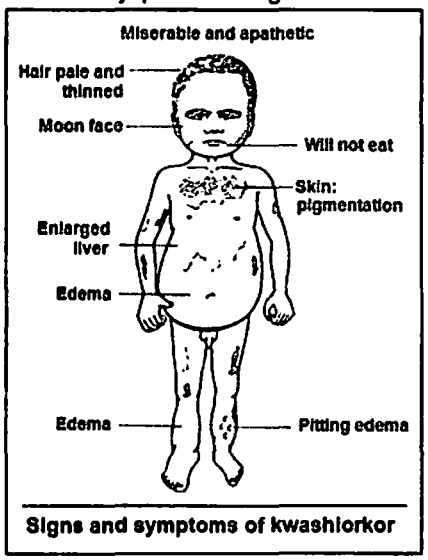
| | | |
|---|---|---|
| Urea (main solute) | 20-40 | g/d |
| Uric acid | 0.5 | g/d |
| Hippuric acid | 0.7 | g/d |
| Ammonia | 0.7 | g/d |
| Creatinine | 0.7-1.7 | g/d |
| Creatine | 0-0.2 | g/d |

         - **In feces:** One gram / day is excreted in feces.
         - **In milk** and menstrual fluids in female.

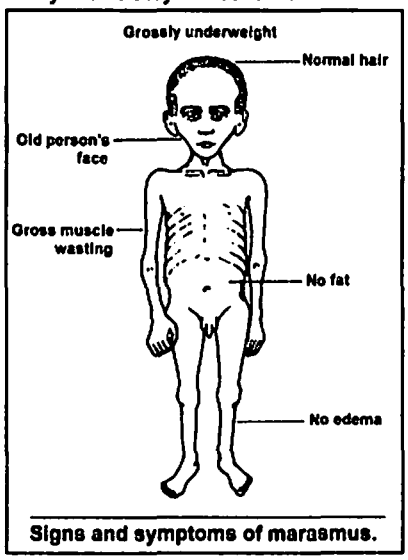
   **b) Positive and negative nitrogen balance:**
      1) **Positive nitrogen balance:** means that nitrogen intake is greater than nitrogen loss. It occurs in conditions where the formation of tissue proteins is increased e.g. growing children and muscle training.
      2) **Negative nitrogen balance:** means that nitrogen intake is less than nitrogen loss. It occurs in conditions where breakdown of tissue proteins is increased e.g. diabetes mellitus and starvation.

4. **Protein-calorie malnutrition:**
   a) In developed countries, protein-calorie malnutrition is seen most frequently in hospital patients with chronic illness or in individuals who suffer major trauma, severe infection, or the effects of major surgery. Such highly catabolic patients frequently require intravenous administration of nutrients.
   b) In under developed countries, an inadequate intake of protein and / or energy may be observed. Individuals show a variety of symptoms, including a depressed immune system with a reduced ability to resist infection. Death from secondary infection is common. Two extreme forms of malnutrition are Kwashiorkor and marasmus.

1) **Kwashiorkor:** This is a disease resulting from deficiency of dietary protein only. It leads to growth retardation, anemia, edema, vomiting and anorexia (loss of appetite).
2) **Marasmus:** this is a disease resulting from deficiency of dietary protein together with dietary carbohydrate and fat.



Signs and symptoms of kwashiorkor



Signs and symptoms of marasmus.

3) **Malnutrition of cancer and AIDs:** Patients with cancer, HIV infection (AIDS) and a number of chronic diseases are frequently undernourished. This condition is called **cachexia.** It is due to:
   - Increased **catabolism of tissue proteins** due to secretion of **cytokines** in response to cancer and infection.
   - Patients are **hypermetabolic** with high basal metabolic rate (BMR). This due to consumption of excess ATP.
   - Patients are **thermogenic** (feeling of hotness) due to increased stimulation of uncoupler proteins by cytokines. This leads to producing energy without incorporation it into ATP synthesis.

V. ***Micronutrients requirements in human:*** They include vitamins and minerals.

A. **Vitamin requirements:**

1. Vitamins are organic nutrients, which are required in small quantities for normal metabolism. They cannot be synthesized by the body in adequate amounts. Humans require either milligram or microgram quantities of each vitamin per day.
2. Vitamins carry out specific biochemical functions. (For details: see chapter of vitamins). Summary of functions, deficiency syndrome and dietary sources is summarized in the following tables:

## Essential fat-soluble vitamins: Summary of major characteristics.

| Vitamin/ Provitamin[1] | Metabolism[2] | Active Metabolite: Physiologic Function | Deficiency Syndrome or Symptoms | Toxicity Syndrome or Symptoms | Sources[3] |
|---|---|---|---|---|---|
| Vitamin A<br>Provitamin: β-carotene<br>Vitamin: retinol | Transported in lymph as retinyl esters in blood bound to retinol-binding protein and prealbumin. | 11-*Cis* retinal is a constituent of rhodopsin and other light-receptor pigments. Unknown metabolites (retinoic acid?) are required for growth and differentiation of epithelial, nervous, and bone tissues. | Children: poor dark adaptation, xerosis, keratomalacia, growth failure, death.<br>Adults: night blindness, xeroderma. | Hypervitaminosis A: headache, dizziness, nausea, skin sloughing, bone pain. | Highly pigmented vegetables (containing carotenes), fortified margarine. |
| Vitamin D<br>Provitamins: ergosterol (plants, yeast) and 7-dehydrocholesterol (skin)<br>Vitamins $D_2$ (ergocalciferol) and $D_3$ (cholecalciferol) | Provitamins converted to vitamins by ultraviolet irradiation. Vitamins hydroxylated in liver to 25-hydroxyvitamin D and in kidney to 1,25-dihydroxyvitamin D and other metabolites. | 1,25-Dihydroxyvitamin $D_3$ is major hormonal regulator of bone mineral (calcium and phosphorus) metabolism. | Children: rickets.<br>Adults: osteomalacia. | Hypervitaminosis D: hypercalcemia, hypercalciuria, nephrocalcinosis. | Fortified milk: sunlight on skin. |
| Vitamin E<br>Tocopherols, tocotrienols | Generally unknown. | Active metabolite unknown. Functions as an antioxidant. | Children: anemia in premature infants.<br>Adults: no known syndrome. | Undefined. Megadose intake reported to induce blurred vision, headaches. | Vegetable seed oils are major source. |
| Vitamin K<br>$K_1$ (phylloquinone), $K_2$ (menaquinone), others | Generally undefined. | Active metabolite unknown but probably hydroquinone derivative. Activates blood clotting factors II, VII, IX, and X by γ-carboxylating glutamic acid residues; also carboxylates bone and kidney proteins. | Infants: hemorrhagic disease of newborn.<br>Adults: defective blood clotting. Deficiency symptoms can be produced by coumarin anticoagulants and by antibiotic therapy. | Can be induced by water-dispersible analogs: hemolytic anemia, liver damage. | Synthesized by intestinal bacteria. |

## Essential water-soluble vitamins: Summary of major characteristics.

| Vitamin | Coenzymes | Biochemical or Physiologic Function[1] | Deficiency Syndrome or Symptoms[2] (and Associated Diet) | Sources[3] |
|---|---|---|---|---|
| Niacin (nicotinic acid, nicotinamide) | Nicotinamide adenine dinucleotide (NAD); nicotinamide adenine dinucleotide phosphate (NADP). | Electron (hydrogen) transfer reactions carried out by dehydrogenase enzymes, eg, pyruvate dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase. | Pellagra (milled corn). | Protein foods containing tryptophan, in addition to niacin sources in note[3]. |
| Thiamin (vitamin $B_1$) | Thiamin pyrophosphate (TPP). | Oxidative decarboxylation of α-keto acids (pyruvate and α-ketoglutarate dehydrogenases) and 2-keto sugars (transketolases). | Beriberi (milled rice); Wernicke-Korsakoff syndrome (alcohol). Antagonized by thiaminase in raw fish. | |
| Riboflavin (vitamin $B_2$) | Flavin adenine dinucleotide (FAD); flavin mononucleotide (FMN). | Electron (hydrogen) transfer reactions (eg, acyl-CoA dehydrogenase). | Cheilosis. | |
| Pantothenic acid | CoA. | Acyl transfer reactions involving CoA or fatty acid synthase complex. | | |
| Vitamin $B_6$, pyridoxine, pyridoxal, pyridoxamine | Pyridoxal phosphate. | Transamination and decarboxylation via Schiff base (many aminotransferase and decarboxylase enzymes). | Low serum levels are associated with pregnancy and oral contraceptive agents. Antagonized by isoniazid, penicillamine, and other drugs. | |
| Biotin | N-Carboxybiotinyl lysine. | $CO_2$ transfer reactions of carboxylase coenzymes (eg, pyruvate carboxylase, acetyl-CoA carboxylase). | Induced by avidin, a protein in raw egg whites, or by antibiotic therapy. | Synthesized by intestinal microorganisms. |
| Vitamin $B_{12}$ (cobalamin) | Methylcobalamin; 5'-deoxyadenosyl cobalamin. | Methylation of homocysteine to methionine; conversion of methylmalonyl-CoA to succinyl-CoA. | Megaloblastic anemia, methylmalonic aciduria, peripheral neuropathy (strict vegetarian diet). Pernicious anemia induced by lack of intrinsic factor. | Animal foods (eg, meat). |
| Folic acid (folacin) | Derivatives of tetrahydrofolic acid. | One-carbon transfer reactions, eg, purine nucleotide and thymidylate synthesis. | Megaloblastic anemia. | |
| Ascorbic acid (vitamin C) | Unknown. | Antioxidant; collagen biosynthesis; tyrosine catabolism (?). | Scurvy (lack of fresh fruits and vegetables). | Fresh fruits (especially citrus) and vegetables. |

## B. Mineral requirements:

1. The minerals required for physiologic functions may be divided into 2 groups:
   *a)* Macrominerals which are required in amounts greater than 100 mg / day.
   *b)* Microminerals (trace elements): which are required in amounts less than 100 mg / day.
   (For details: see chapter of minerals, part III).
2. The following tables summarize both macro and microminerals.

**Essential microminerals (trace elements): Summary of major characterestics.**

| Elements | Functions | Metabolism | Deficiency Disease or Symptoms | Toxicity Disease or Symptoms[1] | Sources[2] |
|---|---|---|---|---|---|
| Chromium | Trivalent chromium, a constituent of "glucose tolerance factor." | | Impaired glucose tolerance; secondary to parenteral nutrition. | | |
| Cobalt | Constituent of vitamin $B_{12}$. | As for vitamin $B_{12}$. | Vitamin $B_{12}$ deficiency. | | Foods of animal origin. |
| Copper | Oxidase enzymes: cytochrome c oxidase, ferroxidase, etc. | Transported by albumin; bound to ceruloplasmin. | Anemia (hypochromic, microcytic); secondary to malnutrition, Menke's syndrome. | Rare; secondary to Wilson's disease. | |
| Iodine | Thyroxine, triiodothyronine. | Stored in thyroid as thyroglobulin. | Children: cretinism. Adults: goiter and hypothyroidism, myxedema. | Thyrotoxicosis, goiter. | Iodized salt, seafood. |
| Iron | Heme enzymes (hemoglobin, cytochromes, etc). | Transported as transferrin; stored as ferritin or hemosiderin; excreted in sloughed cells and by bleeding. | Anemia (hypochromic, microcytic). | Siderosis; hereditary hemochromatosis. | Iron cookware. |
| Manganese | Hydrolase, decarboxylase, and transferase enzymes. Glycoprotein and proteoglycan synthesis. | | Unknown in humans. | Inhalation poisoning produces psychotic symptoms and parkinsonism. | |
| Molybdenum | Oxidase enzymes (xanthine oxidase). | | Secondary to parenteral nutrition. | | |
| Selenium | Glutathione peroxidase. | Synergistic antioxidant with vitamin E. | Marginal deficiency when soil content is low; secondary to parenteral nutrition, protein-energy malnutrition. | Megadose supplementation induces hair loss, dermatitis, and irritability. | |
| Zinc | Cofactor of many enzymes: lactic dehydrogenase, alkaline phosphatase, carbonic anhydrase, etc. | | Hypogonadism, growth failure, impaired wound healing, decreased taste and smell acuity; secondary to acrodermatitis enteropathica, parenteral nutrition. | Gastrointestinal irritation, vomiting. | |
| Fluoride[3] | Increases hardness of bones and teeth. | | Dental caries; osteoporosis(?). | Dental fluorosis. | Drinking water. |

**Essential macrominerals: Summary of major characterestics.**

| Elements | Functions | Metabolism[1] | Deficiency Disease or Symptoms | Toxicity Disease or Symptoms[2] | Sources[3] |
|---|---|---|---|---|---|
| Calcium | Constituent of bones, teeth; regulation of nerve, muscle function. | Absorption requires calcium-binding protein. Regulated by vitamin D, parathyroid hormone, calcitonin, etc. | Children: rickets. Adults: osteomalacia. May contribute to osteoporosis. | Occurs with excess absorption due to hypervitaminosis D or hypercalcemia due to hyperparathyroidism, or idiopathic hypercalcemia. | Dairy products, beans, leafy vegetables. |
| Phosphorus | Constituent of bones, teeth, ATP, phosphorylated metabolic intermediates. Nucleic acids. | Control of absorption unknown (vitamin D?). Serum levels regulated by kidney reabsorption. | Children: rickets. Adults: osteomalacia. | Low serum $Ca^{2+}$:P, ratio stimulates secondary hyperthyroidism; may lead to bone loss. | Phosphate food additives. |
| Sodium | Principal cation in extracellular fluid. Regulates plasma volume, acid-base balance, nerve and muscle function, $Na^+/K^+$-ATPase. | Regulated by aldosterone. | Unknown on normal diet; secondary to injury or illness. | Hypertension (in susceptible individuals). | Table salt; salt added to prepared food. |
| Potassium | Principal cation in intracellular fluid; nerve and muscle function, $Na^+/K^+$-ATPase. | Also regulated by aldosterone. | Occurs secondary to illness, injury, or diuretic therapy; muscular weakness, paralysis, mental confusion. | Cardiac arrest, small bowel ulcers. | |
| Chloride | Fluid and electrolyte balance; gastric fluid. | | Infants fed salt-free formula. Secondary to vomiting, diuretic therapy, renal disease. | | Table salt. |
| Magnesium | Constituent of bones, teeth; enzyme cofactor (kinases, etc). | | Secondary to malabsorption or diarrhea, alcoholism. | Depressed deep tendon reflexes and respiration. | Leafy green vegetables (containing chlorophyll). |

## VI. *Dietary Recommendations:*

Dietary goals are a nutritional guidelines designed to decrease diseases related to diet.

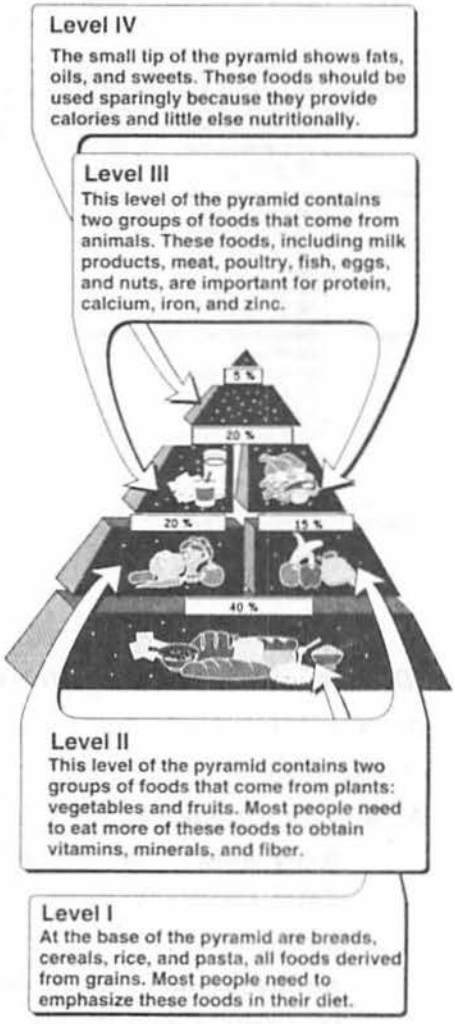
### A. Dietary principles:

1. **Body weight:** achieve and maintain an appropriate body weight.
2. **Total fat:** Reduce the total calories from fat to no more than 30% of total calories.
3. **Saturated fats:** reduce the saturated fats to no more than one third of fat intake or less than 10% of total calories.
4. **Monounsaturated and polyunsaturated fats:** Increase polyunsaturated fats to no more than 10% of total calories and monounsaturated fats to 10% of calories. These fatty acids should include ω3 fatty acids.
5. **Complex carbohydrates:** increase complex carbohydrates to 50-60% of total calories.
6. **Simple carbohydrates:** as glucose and sucrose should be reduced.
7. **Fibers:** Increase dietary fiber to 20-30 g/day.
8. **Cholesterol:** reduce cholesterol intake to less than 300 mg/day.
9. **Salt:** decrease daily intake of salt (sodium chloride) to 3 to 8 g/day or 2400 to 3000 mg sodium per day.

10. **Alcohol:** Apart of religious prohibition and if you drink, limit alcohol intake to no more than one drink for women or two drinks for men per day.

**B. <u>Food guide pyramid</u>**

1. The dietary principles described above focus on the amount of specific nutrients that should be contained in the diet. By contrast the food guide pyramid, formulated by the U.S. Department of agriculture is an educational tool for the lay public that outline the kinds of foods to each day. The pyramid emphasizes foods from food groups shown in level I and II of the pyramid (bread, cereal, rice and pasta, vegetables and fruits). Each of these groups provides some, but not all, of the nutrients needed daily. Foods in one group cannot be substituted for foods in another- in short, a variety of foods from all levels of the pyramid.




Food Guide Pyramid.

## VII. *Obesity:*

**A. <u>Definitions</u>:**

1. **Body mass index (BMI):** is the body weight (in kilograms) divided by the square of the height (in meters).
2. **Ideal body weight (IBW):** is the body weight with the lowest mortality and morbidity. Such body processes:
   a) Normal body mass index ($kg/m^2$) = 20-25.
   b) Normal values of body fat: 12-18% Of body weight in men and 18-25% of body weight in women.
3. **Over weight:** It is a body weight up to 20% above ideal body weight (Body mass index ($kg/m^2$) = 25-30.
4. **Obesity:** It is the body weight 20% or more above ideal body weight. (Body mass index ($kg/m^2$) > 30.

**B. Cuases of obesity:**

1. The major cause of weight gain is the ***consumption of calories*** in excess of daily energy requirements. This due to bad eating habits and environmental factors.
2. ***Endocrine diseases*** such as hypothyrodism or Cushing's disease (overproduction of corticosteroids) are rare cause.
3. Mal-development of the nervous system ***hunger control centers*** in the hypothalamus.
4. ***Genetic causes:*** there is a gene called OB gene produced in adipocytes. It encodes for protein of 146 amino acids called ***leptin.*** This leptin has receptors in hypothalamus. Defective synthesis of leptin leads to obesity, diabetes mellitus and reduced activity and metabolism.

**C. Effects of obesity:**

1. In most common type of obesity, the number of adipocytes of the body does not increase. They just get larger as they become enlarged with triacylglycerols.
2. If obesity develops before puberty, an increase in the number of adipocytes can also occur.
3. Obesity can reduce life span because it is a risk factor in development of:
   a) Diabetes mellitus.
   b) Hypertension.
   c) Endometrial carcinoma.
   d) Osteoarthritis.
   e) Gall stone.
   f) Cardiovascular diseases.

**D. Treatment of obesity:**

1. The only effective treatment of obesity is **reduction in calories** ingestion.
2. **Increase physical activity.**
3. **Behavior modification.**
4. **Surgery:** to limit the size of stomach may be recommended for patient over 100% above IBW.

# Chapter 12 — *Physical chemistry*

## *Composition of matter*

### I. *Definitions:*

**A. <u>An element:</u>**

1. Is a substance that is formed of only one type of atoms.
2. Elements are either metals e.g. iron or non metals e.g chlorine.

**B. <u>An atom:</u>**

1. Any atom contain 3 types of particles
   *a)* **Protons:** Positively charged particles.
   *b)* **Neutrons:** Neutral charged particles.
   *c)* **Electrons:** Negatively charged particles.
2. Protons and neutrons are located in the nucleus, while electrons are located in certain orbits around nucleus.
3. The number of protons is equal to the number of electrons.

**C. <u>Atomic weight (atomic mass)</u>:**

1. It is the number of protons and neutrons.
2. Atomic weight determines the physical properties of the element.

**D. <u>Atomic number:</u>**

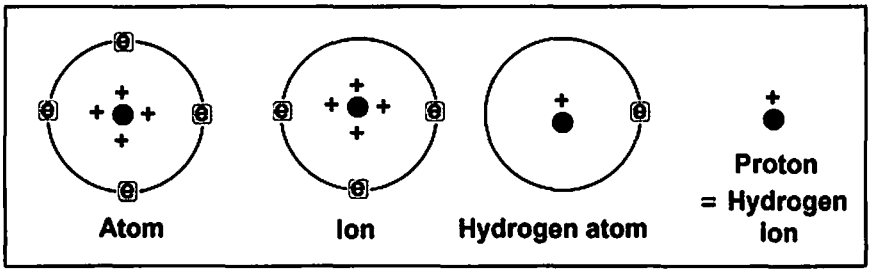
1. It is the number of protons only (and it is equal to electron number).
2. Atomic number determines the chemical properties of the element.

**E. <u>An ion:</u>**

Is an atom, which one or more electrons is removed (positive ion) or added (negative ions).

**F. <u>Hydrogen ion = proton:</u>**

Hydrogen atom formed of one proton and one electron. When the electron is removed, the remaining proton will form hydrogen ion.




### II. *Isotopes:*

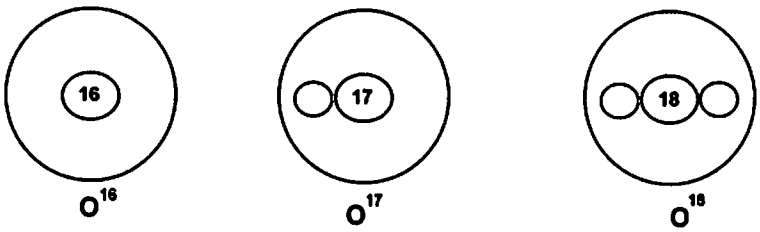
**A. <u>Definition:</u>**

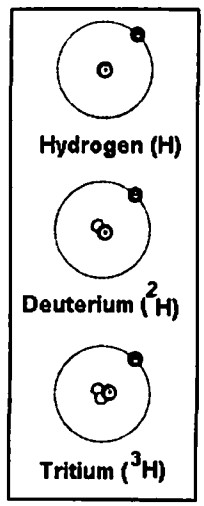
1. These are different forms of the same element that have the same atomic number but differ in atomic weight.

2. They occupy the same position in the periodic table.
3. They have the same chemical properties but differ in physical properties.

**B. Types: Isotopes are of two types:**

1. **Stable isotopes:** e.g. Oxygen 16,17 and 18: $O^{16}$, $O^{17}$,$O^{18}$ .
2. **Radioactive isotopes:** They emit radiations from the nucleus: α and β particles and γ-rays.
   - *a)* **α Particles:** Positively charged particle: 2 protons & 2 neutrons (nucleus of helium atom ($^4{}_2He$)).
   - *b)* **β-Particles:** Negatively charged electrons.
   - *c)* **γ-Rays:** Electromagnetic radiation.




**C. Uses of isotopes:**

1. **Diagnosis:**
   - e.g. $I^{131}$ is used in diagnosis of thyroid gland diseases.
2. **Treatment:**
   - e.g. many cancers which cannot be treated by operation may be treated by radioactive materials.
3. **Research:**
   - e.g. A radioactive material can be introduced into the body and traced to know its fate in the body.

# *Acids, alkalies, and bases*

## I. *Acids:*

**A. Definition:**

Acids are substances that give hydrogen ions or protons in solution:

$$\underset{\text{Hydrochloric acid}}{HCl} \rightarrow \underset{\text{Proton}}{H^+} + \underset{\text{Chloride ion}}{Cl^-}$$

**B. Types:**

1. **Strong acids:**

   Is that acid which dissociates completely in solution e.g.

   $$HCl \rightarrow H^+ + Cl^-$$

   so it gives a large number of protons ($H^+$) in solution.

2. **Weak acid:**

   Is that acid which ionizes slightly in solution e.g.

   $CH3\text{-}COOH\ (Acetic\ acid) \rightarrow CH_3\text{-}COO^- + H^+ \rightarrow CH_3\text{-}COOH$

   Such acid gives a low number of protons ($H^+$) in solution.

C. **True and titratable acidity:**

1. **True acidity:** it is the concentration of $H^+$ ions in a solution or it is the pH of the solution.
2. **Titratable acidity:** it is the concentration of hydrogen ions in a solution available for ionization although not ionized at a time. This can be measured by titrating acid against base.

## II. *Alkalies:*

A. **Definition:**

**Alkalis** are substances that give ($OH^-$) hydroxyl ions in solution:

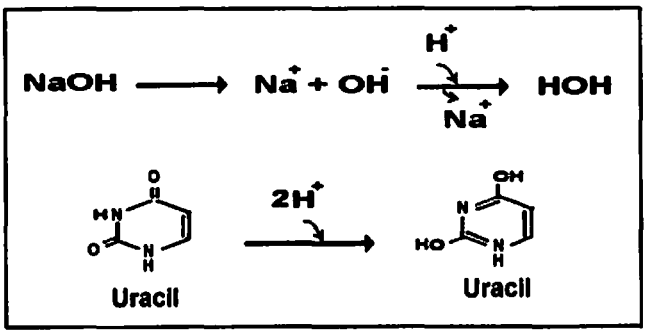
| NaOH | → | $Na^+$ | + | $OH^-$ |
|---|---|---|---|---|
| Sodium hydroxide | | Sodium ions | | Hydroxyl ions |

B. **Types:**

1. **Strong alkali:** Is that alkali which dissociates completely in solution (e.g. NaOH and KOH).
2. **Weak alkali:** Is that alkali which ionizes slightly in solution (e.g. ammonium hydroxide: $NH_4OH$).

## III. *Base:*

A. **Definition:** It is a substance, which accepts ($H^+$) proton. e.g. sodium and uracil.




Note: All alkalies are bases (e.g. NaOH) but not all bases are alkalis.

B. **Conjugate base:**

It is that part of acid which remains after removal of ($H^+$) proton e.g.

| $CH_3COOH$ | ⇆ | $CH_3COO^-$ | + | $H^+$ |
|---|---|---|---|---|
| *Acetic acid* | | *conjugate base (acetate)* | | *Proton* |

## IV. *Amphoteric substances:*

These are substances, which act as an acid (proton donor) or as a base (proton acceptor) e.g. $H_2O$, amino acids.

$$H_2O \leftrightarrows H^+ + OH^- \quad (acid)$$

$$H_2O \leftrightarrows H_3O \quad (base)$$

# *Law of mass action*

## I. *Introduction:*

**A.** The rate (velocity) of reversible reaction is directly proportional to the concentrations of the reacting substances e.g.

$$A + B \leftrightarrows C + D$$

**B.** The velocity ($V_1$) of the reaction to the left is proportional to the concentration of A and B.

$$\therefore V_1 \propto [A] \times [B]$$

**C.** The velocity ($V_2$) of the reaction to the right is proportional to the concentration of C and D.

$$\therefore V_2 \propto [C] \times [D]$$

$\therefore$ $V_1$ = constant ($K_1$) x [A] x [B]

and $V_2$ = constant ($K_2$) x [C] x [D]

at equilibrium $V_1 = V_2$

$\therefore$ ($K_1$) x [A] x [B] = ($K_2$) x [C] x [D]

$$\therefore \frac{[C] \times [D]}{[A] \times [B]} = \frac{K_1}{K_2} = K_{eq}$$

**D.** **<u>Ionization of acids:</u>**

1. The ionization (dissociation) of an acid e.g. acetic acid ($CH_3COOH$) can be presented as follows:

$$CH_3COOH \leftrightarrows CH_3COO^- + H^+$$

By applying the law of mass action, at equilibrium:

$$\frac{[H^+] \times [CH_3COO^-]}{[CH_3\text{-}COOH]} = K_a \text{ (dissociation constant of acid)}$$

2. As the Ka gets bigger, this indicates a strong acid i.e. this acid dissociates into large number of $H^+$ and conjugate base radicals and vice versa.

## II. *pK of an acid:*

It is the negative logarithm of the dissociation constant of the acid to the base 10.

- If the $K_1$ of acid A (strong acid) is $10^{-2}$ , its pK will be = 2.
- If the $K_2$ of acid B (weak acid) is $10^{-6}$ , its pK will be = 6.
- **Thus the smaller the pK, the stronger the acid.**

## III. *pH* (It is the negative logarithm of hydrogen ions concentration to the base 10).

### A. Explanation:

1. At equilibrium of water:

$$H_2O \leftrightarrows H^+ + OH^-$$

2. The amount of ions present in a sample of pure water is very small:
3. Each liter of water contains 0.0000001 ($10^{-7}$) gram $H^+$ .
4. Each liter of water contains 0.0000001 ($10^{-7}$) gram $OH^-$.
5. According to law of mass action:

$$\frac{[H^+] \times [OH^-]}{[H_2O]} = K_W \text{ (dissociation constant of water)}$$

$$\frac{10^{-7} \times 10^{-7}}{1} = K_W$$

$\therefore$ $K_W$ of water = $10^{-14}$

6. Thus in any water solution the $[H^+] \times [OH^-] = 10^{-14}$
7. Any excess of $[H^+]$ is associated with decrease in $[OH^-]$ and vice versa.
8. As hydrogen and hydroxyl ions in water are very small and both are equal, pure water which contains $10^{-7}$ $H^+$ g/L is considered a neutral solution.
   *a)* If hydrogen ion concentration increases (or $OH^-$ decreases) e.g. $10^{-6}$, $10^{-5}$, $10^{-4}$, $10^{-3}$, $10^{-2}$, $10^{-1}$, and $10^{-0}$ this indicates acidity.
   *b)* If hydrogen ion concentration decreases (or $OH^-$ increases) e.g. $10^{-8}$, $10^{-9}$, $10^{-10}$, $10^{-11}$, $10^{-12}$, $10^{-13}$, and $10^{-14}$ this indicates alkalinity.
9. For simplicity to indicate neutrality, acidity, and alkalinity, we use pH term.

### B. Definitions:

1. **pH of a solution:**
   *a)* It is the negative logarithm of hydrogen ions concentration to the base 10.

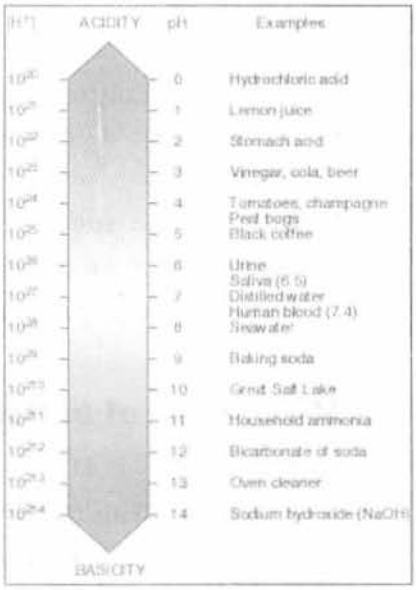
$$\mathbf{pH = - Log\ [H^+]\ to\ the\ base\ 10}$$

   *b)* The smaller the pH, the increase the acidity.

| $[H^+]$ | $10^0$ | $10^{-1}$ | $10^{-2}$ | $10^{-3}$ | $10^{-4}$ | $10^{-5}$ | $10^{-6}$ | $10^{-7}$ | $10^{-8}$ | $10^{-9}$ | $10^{-10}$ | $10^{-11}$ | $10^{-12}$ | $10^{-13}$ | $10^{-14}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| pH | zero | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |

Acidity ← Neutral → Alkalinity

2. pH of blood:




*a)* Blood pH is normally 7.4 ± 0.03 (7.37 - 7.43)

1) A decrease in blood pH is called acidosis.

2) An increase in blood pH is called alkalosis.

*b)* Slight change in blood pH will affect the functions of the body e.g. any enzyme needs special pH for its maximum action.

*c)* Severe change in blood pH may lead to death.

*d)* The blood pH is kept within very narrow range due to the presence of buffers in both blood and tissues.

## IV. *Henderson-Hasselblach equation*:

A. This equation represents the relationship between pH and pK (acid dissociation constant) of a weak acid. A weak acid: HA ionizes as follows:

$$HA \rightleftarrows H^+ + A^-$$

B. According the law of mass action:

1. $$\frac{[H^+]\ x\ [A^-]}{[HA]} = K$$

$$\therefore [H^+]\ x\ [A^-] = K\ [HA]$$

By dividing both sides by $[A^-]$

$$\therefore [H^+] = K\ \frac{[HA]}{[A^-]}$$

2. By taking the log of both sides.

$$\text{Log}\ [H^+] = \text{Log}\ (K\ \frac{[HA]}{[A^-]}) = \text{Log}\ K + \text{Log}\ \frac{[HA]}{[A^-]}$$

3. By multiplying both sides by -1

$$\therefore -\text{Log}\ [H^+] = -\text{Log}\ K - \text{Log}\ \frac{[HA]}{[A^-]}$$

$\therefore$ $-\text{Log}\ [H^+] = pH$

$\therefore$ $-\text{Log}\ K = pK$

$$\therefore \text{pH} = \text{pK} - \text{Log} \frac{[HA]}{[A^-]}$$

# Buffers

## I. Definition:

A. Buffer is a solution, which resists change in pH when an acid or alkali is added to it.

B. Buffers are usually a mixture of a weak acid with salt of strong base, or a mixture of a weak base and its salt of strong acid e.g. carbonic acid and sodium bicarbonate ($H_2CO_3$ / $NaHCO_3$).

## II. Mechanism of buffer action:

A. If the buffer is $H_2CO_3$ / $NaHCO_3$.

1. When alkali (NaOH) is added: $NaOH + H_2CO_3 \rightarrow NaHCO_3 + HOH$
2. When acid (HCl) is added: $HCl + NaHCO_3 \rightarrow H_2CO_3 + NaCl$

B. In either case the change in hydrogen ion concentration (pH) is relatively smaller than if the buffer was not present.

## III. Body buffer:

Buffers of the body are either present in plasma and extracellular tissue or inside the RBCs. These buffers keep hydrogen ion concentration within narrow range suitable for life 7.4 ± 0.03.

A. **Plasma buffers e.g.**

1. Bicarbonate buffer : $H_2CO_3$ / $NaHCO_3$.
2. Phosphate buffer: $Na_2HPO_4$ / $NaH_2PO_4$.
3. Plasma proteins: sodium proteinate / H protein.

B. **RBCs buffers e.g.**

1. Bicarbonate buffer: $H_2CO_3$ / $KHCO_3$.
2. Hemoglobin buffer: KHb / HHb.
3. Oxyhemoglobin buffer: $KHbO_2$ / $HHbO_2$

# Solutions, Units of Mass and Units of Concentration

## I. Solutions:

A. If we dissolve sodium chloride (NaCl) in water, it will form true solution.

**B.** The sodium chloride is called solute and the water is called solvent.

**II. *Units of mass:*** Mass is expressed in terms of grams, moles or equivalents.

**One mole:** It is the amount (weight) of substances (in grams) equal to its molecular weight.

(The molecular weight is the sum of all atomic weights of all atoms in a compound e.g. molecular weight of NaOH = 23 + 16 + 1

∴ One mole of NaOH = 40 grams.

**III. *Units of concentration:***

The concentration of a solution is expressed in molarity or normality.

**A. Molar solution:**

1. Is the solution, which contains one mole of the solute dissolved in one liter of solvent.
2. ∴ Molar solution of NaOH = 40 grams NaOH dissolved in one liter water.

**B. Normal solution:**

1. Is the solution, which contains one equivalent of the solute, dissolved in one liter of solvent.
2. e.g. Molecular weight of $H_2SO_4$ = 98 and it contains 2 hydrogen atoms.

   ∴Normal solution of $H_2SO_4$ = 98/2 = 49 grams $H_2SO_4$ Dissolved in one liter water.

# *Crystalloids, Colloids and suspensions*

| < 1.0 nm | 1 - 200nm | | >200 nm |
|---|---|---|---|
| Crystalloids | Colloids | | Suspension |
| | Emulsoids | Suspensoids | |

**I. *Definitions:***

**A. Crystalloids:**

Are solutions in which the size of particles is less than one nanometer.

**B. Colloids:**

Are solutions in which the size of particles ranges from one to 200 nanometers (1 to 200 nm). They are either emulsoids or suspensoids.

**C. Suspensions:**

Are solutions in which the size of particles is more than 200 nm.

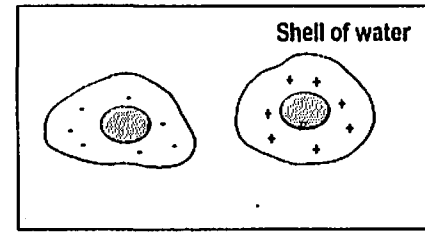
**N.B.:** Nanometer = 0.000000001 ($10^{-9}$) meter.

**II. *Colloids***

Any colloid is formed of particles (dispersed phase) which are distributed in a solvent (dispersion medium).

A. **Types of colloids**: There are two types of colloids; emulsoids and suspensoids.

1. **Emulsoids:**

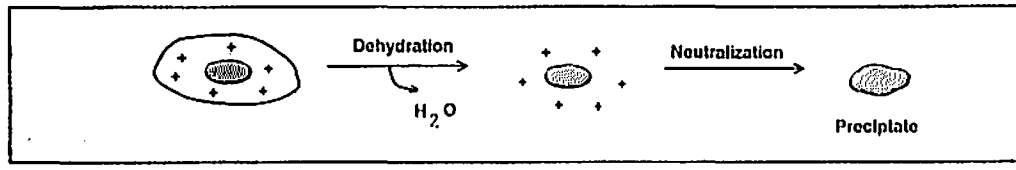



*a)* They are also called lyophilic or hydrophilic colloids (if water is the dispersion medium).

*b)* The dispersed particles are surrounded by 2 stability factors: a positive or negative charges and a shell of dispersion medium e.g. water.

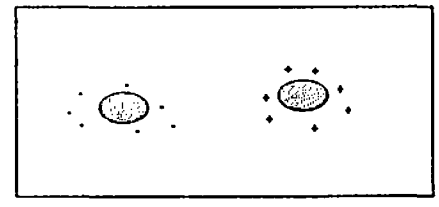
*c)* Emulsoids are stable and not easily precipitated.

*d)* Emulsoids can be precipitated by dehydration (removal of water shell) followed by neutralization of surrounded electric charges by adding particles with the opposite charges.




2. **Suspensoids:**

*a)* They are also called lyophobic or hydrophobic colloids (if water is the dispersion medium).



*b)* The dispersed particles are surrounded by only one stability factor which either positive or negative charges (no shell of water).

*c)* Due to absence of water shell, they are not stable and easily precipitated.

*d)* Suspensoids can be precipitated by only neutralization of electrical charges.

B. **General properties of colloids**

1- Tyndall effect.
2- Brownian movements.
3- Viscosity.
4- Osmotic pressuro.
5- Gel formation.
6- Imbibition.
7- Syneresis.

1. **Tyndall effect:** Any colloidal solution appears cloudy to the eye if a beam of light is passed through it. This is due to reflection of light by colloidal particles in solution.
2. **Brownian movements:** This is the continuous and strong vibratory movement due to the bombardment of colloidal particles by the molecules of solvent (like a game of billiards). The smaller particles move more easily than the big ones.
3. **Viscosity (see later):** Emulsoids are more viscous than suspensoids.
4. **Osmotic pressure (see later):** Osmotic pressure caused by colloid solutions is very small due to the large size of colloidal particles.

5. **Gel formation:** many colloids form a gelly-like mass on cooling e.g. gelatin.
6. **Imbibition:** It is the ability of some colloids (e.g. gelatin) to take water and swell.
7. **Syneresis:** The concentration of a gel: concentration of blood clot leads to squeeze serum out.

C. ***Comparison between emulsoids and suspensoids:***

| Emulsoids | Suspensoids |
|---|---|
| 1-Solvent lovers (lyophilic) | 1-Solvent haters (lyophobic) |
| 2-They have 2 stability factors | 2-They have one stability factor |
| 3-Difficult to precipitate | 3-Easily to precipitate |
| 4-More viscous | 4-Less viscous |
| 5-Tyndall effect more marked | 5-Tyndall effect less marked |
| 6-Brownian movement less marked | 6-Brownian movement more marked |
| 7-Example: a) starch solution.<br>b) Egg white solution.<br>c) Protein solution. | 7-Examples: a) Colloidal gold.<br>b) Colloidal iron |

D. **Stability of colloids:**

1. **Factors causing stability of colloids:**
   *a)* **Presence of similar charges** on all particles (repelling each other).
   *b)* **Brownian movement:** keep the particles distributed in the whole system.
   *c)* **Presence of fluid around the particles**. So emulsoids are more stable than suspensoids.
2. **Examples of colloidal stabilizers:** Soap, saponine and gelatin.

# *Solution phenomena*

## I. *Diffusion:*

- Diffusion is the distribution of particles by simple agitation i.e. all molecules are in state of an agitated motion by which diffusion occur.
- If two solutions are poured together without mixing they will diffuse and become one homogenous solution after a short time.

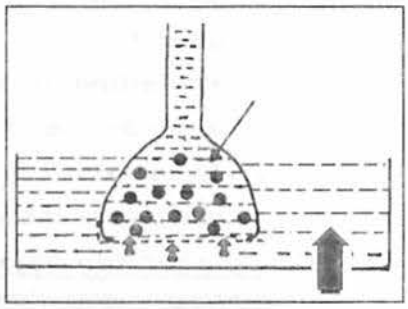
## II. *Osmosis and osmotic pressure:*

A. **Definitions:**

1. **Osmosis:**

   Is the passage of solvent molecules from lower to higher concentration through semi permeable membrane i.e. membrane of certain pores that allows the passage of small particles (solvent

particles) and prevents passage of large particles (solute particles).



2. **Osmotic pressure:**

It is the hydrostatic pressure needed to prevent osmosis.

## B. Factors affecting osmotic pressure:

1. **Number of dissolved particles:**

Crystalloid solutions have a higher osmotic pressure than colloidal solutions. This because crystalloid particles are smaller than colloidal ones.

2. **Number of ions:**

*a)* Ionizable molecules have higher osmotic pressure than non ionizable particles.

*b)* If we have the same number of molecules of glucose (nonionizable), sodium chloride: NaCl (ionizable into sodium and chloride) and calcium chloride:$CaCl_2$ (ionizable into calcium and two chloride ions),Thus:

| | |
|---|---|
| Glucose → 1 | : one osmotic pressure. |
| $NaCl \rightarrow Na^+ + Cl^- \rightarrow 2$ | : two osmotic pressures. |
| $CaCl_2 \rightarrow Ca^{++} + Cl^- + Cl^- \rightarrow 3$ | : three osmotic pressures. |

## C. Physiological importance of osmotic pressure

1. **Urine formation:**

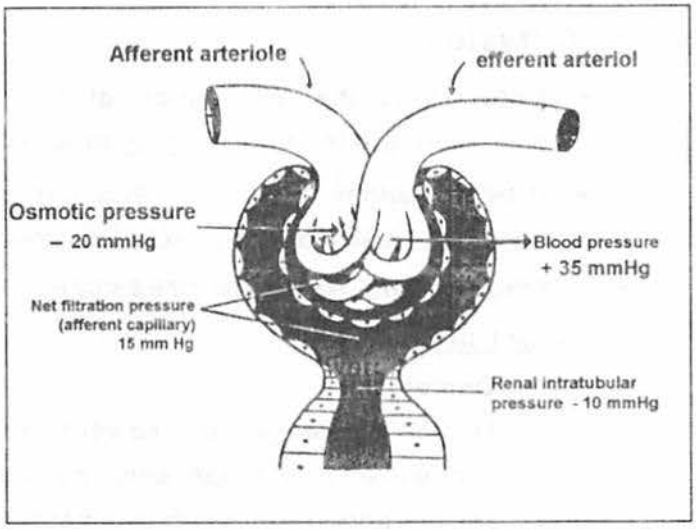
*a)* Inside the glomerular capillaries, there are 2 opposing forces:

1) **Filtration force =** + 35 mm Hg (caused by capillary ***blood pressure).***

2) **Reabsorptive force =** - 20 mm Hg (caused by ***osmotic pressure*** of plasma proteins).

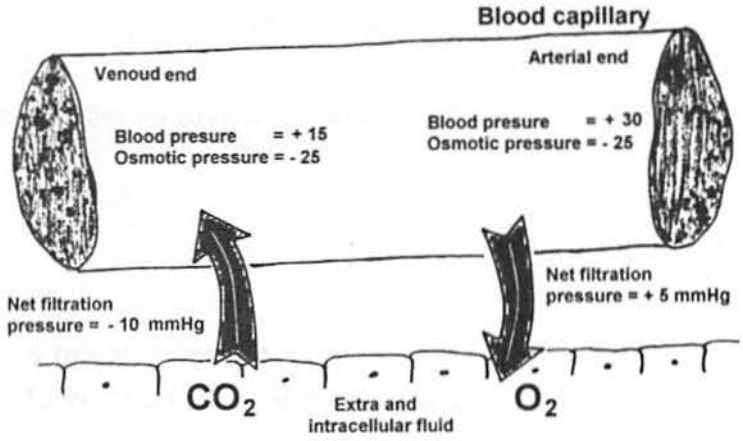
*b)* So, the net filtration pressure = + 35 - 20 = + 15 mm Hg.

*c)* Under conditions of shock where capillary blood pressure is much decreased, filtration stops and anuria results until blood pressure is restored.



2. **Formation and reabsorption of interstitial fluid:**

The interstitial fluid is formed by filtration of the blood plasma at the arterial end of the blood capillaries, and its reabsorption at the venous end.




*a)* At the arterial end, blood pressure is greater than osmotic pressure of plasma proteins. This leads to formation of interstitial fluid (30 mmHg -25 mmHg = + 5 mmHg).

*b)* At the venous end, blood pressure is less than osmotic pressure of plasma proteins. This leads to reabsorption of interstitial fluid (15 mmHg - 25 mmHg = -10 mmHg).

3. **Hemolysis:**

The red blood cells are isotonic with 0.9% NaCl solution i.e. this solution has the same osmotic pressure as that of RBCs and cells neither swell nor shrink.

*a)* If RBCs are put in hypertonic solution (i.e. solution has a higher osmotic pressure than cells), RBCs will loss water and become crenate.

*b)* If RBCs are put in hypotonic solution (i.e. solution has a lower osmotic pressure than cells). RBCs absorb water and swell and hemolysis occurs.

## II. *Viscosity:*

### A. Definition:

It is the resistance offered by the fluid to flow. It is due to the internal friction between molecules of the fluid.

### B. Factors affecting viscosity:

1. **Temperature:**

Viscosity decreases with the rise of temperature and vice versa.

2. **Solute concentration and size:**

Viscosity increases with increase in both concentration and size of solutes and vice versa.

C. **Viscosity of the blood is due** to plasma proteins, red and white cells. It is one of the important factors, which determine blood pressure.

1. In **anemia and hypoproteinemia:** viscosity decreases.
2. In **polycythemia** viscosity increases.

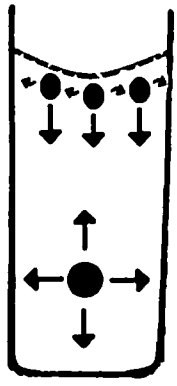
D. **Units of viscosity**

The poise is the unit of viscosity. Absolute viscosity of water at 25°C is **0.895 poise**.

## IV. *Surface tension:*

A. **Definition:**

It is the force which holds the surface molecules of a liquid together and attracts them toward the body of the liquid.



B. **Mechanism of surface tension:**

1. Molecules at the surface are subjected to unbalanced attraction force i.e. attraction toward the body of the liquid only. Thus molecules at the surface are not freely mobile.
2. Molecules in the interior of a liquid are subjected to attraction force in all directions. Thus molecules in the interior of a liquid are freely mobile.

C. **Emulsification:**

1. This is the breakdown of large fat globules in water into small ones to form emulsion.
2. Substances which lower the surface tension of water can act as emulsifying agent e.g.
   *a)* Bile salts.
   *b)* Soap.
   *c)* Proteins.

## V. *Hydrotrophy:*

A. **Definition:**

It is the capacity of certain substance to make water insoluble substance more soluble e.g. bile salts render fats and fatty acids soluble in water, so, they are easily absorbed.

B. **Hydrotropic factors:**

Substances, which make water insoluble substance more soluble in water e.g. bile salts, phospholipids and glucuronic acid.

C. **Lipotropic factors:**

Are substances, which help the mobilization of fats from the liver and so prevent fatty liver, e.g. methionine, choline, inositol...etc.

## VI. *Adsorption:*

It is capacity of substance to make other substance closely attached to its surface (=adsorbed on it). This is due to the presence of attractive forces on the surface of adsorbing agent.

## VII. *Elution:*

Is the recovery of adsorbed material from adsorbing agent.

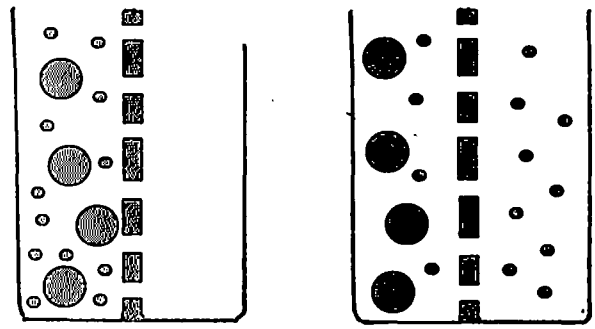
## VIII. *Dialysis:*

A. **Definition:**

It is the separation of colloids from crystalloids using a semi permeable membrane.

B. **Mechanism of dialysis:**

1. Crystalloids can pass through semi-permeable membrane while colloids cannot pass due to the large size of their particles e.g. proteins (colloids) have a high molecular weight. A mixture of proteins (colloids) and salts (crystalloids) can be separated by dialysis by using semi permeable membrane. Crystalloids can pass through this membrane, while colloids cannot due to the large size of their particles.



**Before dialysis** **After dialysis**

C. **Medical importance of dialysis:**

Dialysis has a medical importance. It can be used in cases of renal failure **(renal dialysis)**. The blood passes through dialyzing machine to get red of waste products **(crystalloids)** and preserving the plasma proteins **(colloids)**.

## IX. *Osmolarity and osmolality:*

### A. Definition:

These two terms define the relationship between concentration of substance and volume of solvent (osmolarity) or mass of solvent (osmolality):

1. **Osmolarity:**

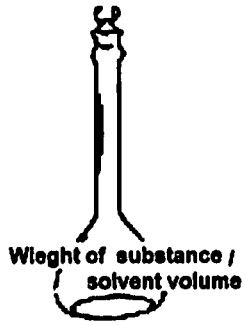
   It is the concentration of a substance per volume solution (concentration of substance / liter water). As the volume varies with change in temperature, so osmolarity depends on temperature.

2. **Osmolality:**

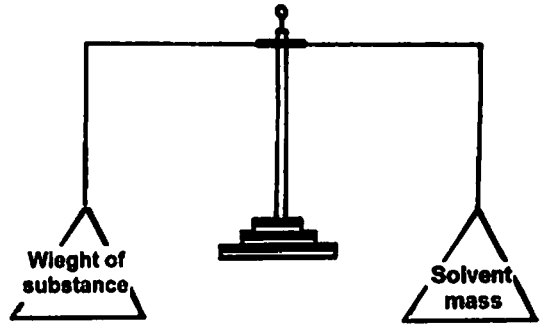
   It is the concentration of a substance per mass solution (concentration of substance / Kg water).

### B. An osmometer:

It is an instrument for measuring osmolality.




**Osmolarity**

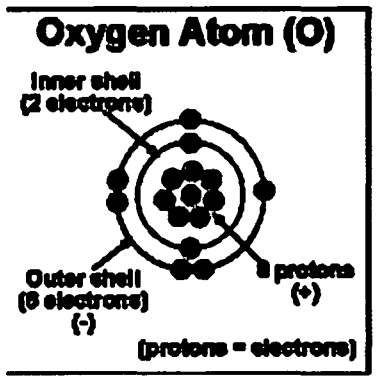


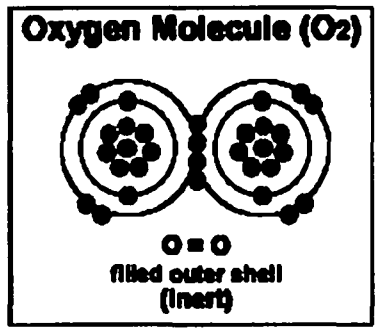

**Osmolality**

# Covalent and Noncovalent Bonds

## I. Covalent Bonds:

A. Atoms consist of a nucleus (neutrons & protons) and electrons. The number of protons (positively charged particles) in the atom's nucleus determines the number of electrons (negatively charged particles) surrounding the atom.




B. Electrons are involved in chemical reactions and are the substances that bind atoms together to form molecules. Electrons surround, or "orbit" an atom in one or more shells. The innermost shell is full when it has two electrons. When the first shell is full, electrons begin to fill the second shell. When the second shell has eight electrons, it is full, and so on.

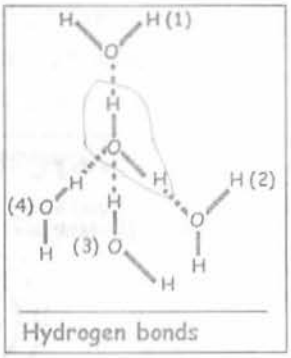
C. The most important structural feature of an atom for determining its chemical behavior is the number of electrons in its outer shell. A substance that has a full outer shell tends not to enter in chemical reactions (an inert substance). Because atoms seek to reach a state of maximum stability, an atom will try to fill its outer shell by:
   1. Gaining or losing electrons to either fill or empty its outer shell.
   2. Sharing its electrons by bonding together with other atoms in order to complete its outer shell.

D. Atoms often complete their outer shells by sharing electrons with other atoms. By sharing electrons, the atoms are bound together and satisfy the conditions of maximum stability for the molecule.

***Covalent bonds are formed by the sharing of electrons in the outer atomic orbital, and they hold the atoms within an individual molecule together. Covalent bonds tend to be very stable and require much energy to break or rearrange.***

II. ***Noncovalent Bonds:*** These are much weaker than covalent bonds. They play an important role in determining many properties of the molecules and how these molecules interact with water and with each other. They include the following types:

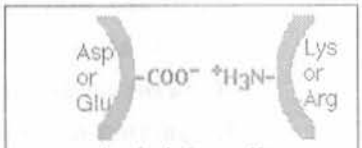
A. **Hydrogen bonds:** In any hydrogen bond, the hydrogen polar molecules, such as water molecules, have a weak, partial negative charge at one region of the molecule (the oxygen atom in water) and a partial positive charge elsewhere (the hydrogen atoms in water).



Hydrogen bonds

1. Thus when water molecules are close together, their positive and negative regions are attracted to the oppositely-charged regions of nearby molecules. The force of attraction, shown here as a dotted line, is called a **hydrogen bond**. Each water molecule is hydrogen bonded to four others.
2. **Multiple hydrogen bonds:**
   *a)* hold the two strands of the DNA double helix together.
   *b)* hold polypeptides together in such secondary structures as the alpha helix and the beta conformation;
   *c)* help enzymes bind to their substrate;
   *d)* help antibodies bind to their antigen
   *e)* help transcription factors bind to each other;
   *f)* help transcription factors bind to DNA .

B. **Ionic interactions:**

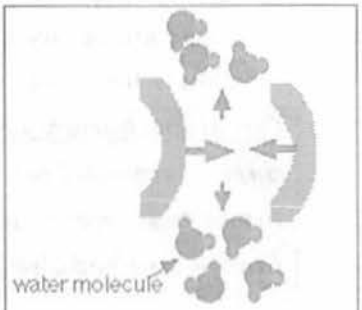


Ionic Interactions

1. At any given pH, proteins have charged groups that may participate in binding them to each other or to other types of molecules. For example, as the figure shows, negatively-charged carboxyl groups on aspartic acid (Asp) and glutamic acid (Glu) residues may be attracted by the positively-charged free amino groups on lysine (Lys) and arginine (Arg) residues.
   *a)* Ionic interactions are highly sensitive to **changes in pH**.

C. **Hydrophobic Interactions:**

1. The side chains (R groups) of such amino acids as phenylalanine and



Hydrophobic Interaction

leucine are nonpolar and hence interact poorly with polar molecules like water. For this reason, most of the nonpolar residues in globular proteins are directed toward the interior of the molecule whereas such polar groups as aspartic acid and lysine are on the surface exposed to the solvent. When nonpolar residues are exposed at the surface of two different molecules, it is energetically more favorable for their two "oily" nonpolar surfaces to approach each other closely displacing the polar water molecules from between them.

2. The strength of hydrophobic interactions is not appreciably affected by changes in pH or in salt concentration.

**D. Van der Waals forces:**

1. It is important to remember that van der Waals' forces are forces that exist between MOLECULES of the same substance. They are quite different from the forces that make up the molecule. For example, a water molecule is made up of hydrogen and oxygen, which are bonded together by the sharing of electrons. These electrostatic forces that keep a molecule intact are existent in covalent and ionic bonding but they are NOT van der Waals' forces.
2. The van der Waals' forces are the forces that exist between the millions of separate water molecules, and not between the hydrogen and oxygen atoms in the case of water.
3. **Dipole-Dipole forces** are one of van der Waals' three forces. Dipole Dipole forces occur in polar molecules, that is, molecules that have an unequal sharing of electrons. For example, HCl comprised of the atom Hydrogen and Chlorine is polar. The Chlorine atom has an extra electron, which came from the hydrogen atom. Because of this, the chlorine part of the molecule is negatively charged, and the hydrogen side of the molecule is positively charged. ie. **H - Cl**

   **+ -**

4. So in a solution where there are thousands of these molecules around that are slightly charged on each side, the molecules naturally orient themselves the accommodate the charge. The positive part of one molecule will move until it is next to the negative part of a neighboring molecule. These forces between molecules tend to make them 'stick' together.

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